dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give tert-butyl{4-[2-(2-(acetylamino)-5-{[(4-nitrobenzyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate (123.7 mg) as a pale yellow solid.

mp. 204-205°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.77-2.91(2H, m), 3.12-3.27(2H, m), 4.49(2H, d, J=5.5Hz), 7.01(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.52(2H, d, J=8.5Hz), 8.21(2H, d, J=8.5Hz), 8.68(1H, t, J=5.5Hz), 9.21(1H, s), 12.40(1H, s).

MS: 540$(M+H)^+$

Step 2

tert-Butyl {4-[2-(2-(acetylamino)-5-{[(4-nitrobenzyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate (135 mg) and TFA (2 ml) were combined at 0°C. The reaction mixture was stirred at room temperature for an hour, and concentrated *in vacuo*. The residue was dissolved in MeOH and $CHCl_3$, and made basic (pH=8) by 1N-NaOH. The mixture was concentrated *in vacuo*. The residual solid was washed with water to give 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide (92.5 mg) as a pale yellow solid.

mp. 120-121°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.65-2.81(2H, m), 3.04-3.21(2H, m), 4.49(2H, d, J=5.5Hz), 5.65(2H, brs), 6.54(2H, d, J=8.0Hz), 6.86(2H, d, J=8.0Hz), 7.54(2H, d, J=8.5Hz), 8.21(2H, d, J=8.5Hz), 8.67(1H, t, J=5.5Hz), 12.39(1H, s).

MS: 440$(M+H)^+$

Step 3

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide (83 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (58.6 mg) and THF (1 ml) were combined under N_2 atmosphere. The reaction

mixture was stirred at r.t. for 2 hours, and concentrated *in vacuo*. The residual solid was washed with AcOEt to give di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[(4-nitrobenzyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate (95.4 mg) as an off-white solid.

mp. 251-253°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.38(9H, s), 1.51(9H, s), 2.16(3H, s), 2.81-2.98(2H, m), 3.16-3.29(2H, m), 4.49(2H, d, J=5.5Hz), 7.12(2H, d, J=8.0Hz), 7.40(2H, d, J=8.0Hz), 7.53(2H, d, J=8.5Hz), 8.20(2H, d, J=8.5Hz), 8.67(1H, t, J=5.5Hz), 9.93(1H, s), 11.44(1H, s), 12.42(1H, s).

MS: 682(M+H)$^+$

Step 4

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[(4-nitrobenzyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate (70 mg) and 4N HCl in 1,4-dioxane solution (1.5 ml) were combined under N_2 atmosphere. The reaction mixture was stirred at r.t. for 14 hours. The solvent was removed *in vacuo*. The residue was washed with AcOEt to give 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide hydrochloride (63.7 mg) as a pale green solid.

mp. 138-140°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.81-3.00(2H, m), 3.17-3.30(2H, m), 4.48(2H, d, J=5.5Hz), 7.12(2H, d, J=8.0Hz), 7.25(2H, d, J=8.0Hz), 7.40(3H, s), 7.55(2H, d, J=8.0Hz), 8.21(2H, d, J=8.0Hz), 8.80(1H, t, J=5.5Hz), 9.81(1H, s), 12.42(1H, s).

MS: 482(M+H)$^+$ free

Production Example 32: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-

(methylsulfonyl)benzyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (120 mg), [4-(methylthio)benzyl]amine (45.4 mg), 1-hydroxybenzotriazole (44 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (59.6 mg) in DMF (2 ml) was stirred at r.t. for 17 hours. The reaction mixture was poured into saturated $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with $CHCl_3$ / AcOEt (1:1) as an eluent to give tert-butyl (4-{2-[2-(acetylamino)-5-({[4-(methylthio)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate (163.5 mg) as an off-white solid.

mp. 182-183°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.45(3H, s), 2.77-2.91(2H, m), 3.09-3.24(2H, m), 4.32(2H, d, J=5.5Hz), 7.02(2H, d, J=8.5Hz), 7.22(4H, s), 7.33(2H, d, J=8.5Hz), 8.54(1H, t, J=5.5Hz), 9.22(1H, s), 12.36(1H, s).

MS: 541$(M+H)^+$

Step 2

Potassium peroxymonosulfate (264 mg) was suspended in water (1 ml) and THF (1 ml), and then tert-butyl (4-{2-[2-(acetylamino)-5-({[4-(methylthio)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate (155 mg) in THF (2 ml) was added dropwise to the suspension at 0°C. The reaction mixture was stirred at r.t. for an hour, and then water was added to the suspension. The solution was extracted with AcOEt (twice). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give tert-butyl

(4-{2-[2-(acetylamino)-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate (140.6 mg) as an off-white solid.

mp. 192.5-193°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.73-2.90(2H, m), 3.11-3.27(2H, m), 3.18(3H, s), 4.47(2H, d, J=5.5Hz), 7.03(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.89(2H, d, J=8.5Hz), 8.68(1H, t, J=5.5Hz), 9.22(1H, s), 12.39(1H, s).

MS: 573(M+H)$^+$

Step 3

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[4-(methylsulfonyl)benzyl]-1,3-thiazole-5-carboxamide was prepared in a similar manner according to Step 2 of Production Example 31.

mp. 78-80°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.65-2.80(2H, m), 3.04-3.22(2H, m), 3.19(3H, s), 4.46(2H, d, J=5.5Hz), 4.82(2H, s), 6.46(2H, d, J=8.0Hz), 6.81(2H, d, J=8.0Hz), 7.53(2H, d, J=8.0Hz), 7.89(2H, d, J=8.0Hz), 8.63(1H, t, J=5.5Hz), 12.39(1H, s).

MS: 473(M+H)$^+$

Step 4

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.16(3H, s), 2.81-2.98(2H, m), 3.18(3H, s), 3.18-3.29(2H, m), 4.46(2H, d, J=5.5Hz), 7.14(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 7.54(2H, d, J=8.5Hz), 7.88(2H, d, J=8.5Hz), 8.67(1H, t, J=5.5Hz), 9.94(1H, s), 11.44(1H, s), 12.41(1H, s).

MS: 715(M+H)$^+$

Step 5

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 94-96°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.85-2.99(2H, m), 3.19(3H, s), 3.19-3.30(2H, m), 4.46(2H, d, J=5.5Hz), 7.13(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.40(3H, s), 7.54(2H, d, J=8.5Hz), 7.89(2H, d, J=8.5Hz), 8.78(1H, t, J=5.5Hz), 9.80(1H, s), 12.41(1H, s).

MS: 515(M+H)$^+$ free

Production Example 33: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[4-(trifluoromethyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.73-2.92(2H, m), 3.12-3.25(2H, m), 4.45(2H, d, J=5.5Hz), 7.01(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.47(2H, d, J=8.5Hz), 7.69(2H, d, J=8.5Hz), 8.64(1H, t, J=5.5Hz), 9.22(1H, s), 12.39(1H, s).

MS: 563(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide was prepared in a similar manner according to Step 2 of Production Example 31.

mp. 199-201°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.63-2.78(2H, m), 3.02-3.18(2H, m), 4.44(2H, d, J=5.5Hz), 4.81(2H, s), 6.46(2H, d, J=8.0Hz), 6.81(2H, d, J=8.0Hz), 7.49(2H, d, J=8.0Hz), 7.69(2H, d, J=8.0Hz), 8.44(1H, t, J=5.5Hz), 12.39(1H, s).

MS: 463(M+H)$^+$

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(trifluoromethyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

mp. 188-190°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.16(3H, s), 2.83-2.97(2H, m), 3.17-3.29(2H, m), 4.44(2H, d, J=5.5Hz), 7.12(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 7.48(2H, d, J=8.0Hz), 7.69(2H, d, J=8.0Hz), 8.63(1H, t, J=5.5Hz), 9.94(1H, s), 11.44(1H, s), 12.40(1H, s).

MS: 705(M+H)$^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 156-158°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.82-2.99(2H, m), 3.18-3.31(2H, m), 4.44(2H, d, J=5.5Hz), 7.12(2H, d, J=8.0Hz), 7.25(2H, d, J=8.0Hz), 7.40(3H, s), 7.51(2H, d, J=8.0Hz), 7.71(2H, d, J=8.0Hz), 8.76(1H, t, J=5.5Hz), 9.81(1H, s), 12.41(1H, s).

MS: 505(M+H)$^+$ free

Production Example 34: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(3-pyridinyl)-1,3-thiazole-5-carboxamide dihydrochloride

Step 1

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylic acid was prepared from 2-(acetylamino)-4-(2-{4-

[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 2 of Production Example 31.

mp. 211.5-212°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.67-2.80(2H, m), 3.09-3.23(2H, m), 6.51(2H, d, J=8.0Hz), 6.85(2H, d, J=8.0Hz), 12.44(1H, brs).

MS: 306(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylic acid (106 mg) was suspended in THF (2 ml) under N_2 atmosphere. Bis(trimethylsilyl)acetamide (0.253 ml) was added to the suspension at r.t., and the mixture was stirred at r.t. for 15 minutes. Then, N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (119 mg) was added to the solution at r.t. The reaction mixture was stirred at r.t. for 20 hours, and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$. The organic solution was washed with 1N-HCl, water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give 2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino](tert-butoxycarbonyl)iminomethyl}amino)phenyl]ethyl}-1,3-thiazole-5-carboxylic acid (115.8 mg) as a pale brown solid.

mp. 221.5-223°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.44(18H, brs), 2.16(3H, s), 2.91(2H, t, J=7.0Hz), 3.26(2H, t, J=7.0Hz), 7.17(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 9.95(1H, brs), 11.43(1H, brs), 12.48(1H, s).

MS: 548(M+H)$^+$

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(3-pyridinylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in

a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.19(3H, s), 2.87-3.00(2H, m), 3.19-3.32(2H, m), 7.16(2H, d, J=8.5Hz), 7.35(1H, dd, J=8.5, 4.5Hz), 7.41(2H, d, J=8.5Hz), 8.07(1H, m), 8.28(1H, dd, J=4.5, 1.5Hz), 8.81(1H, d, J=1.5Hz), 9.93(1H, s), 10.11(1H, s), 11.43(1H, s), 12.51(1H, s).

MS: 624(M+H)$^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.21(3H, s), 2.84-3.07(2H, m), 3.19-3.39(2H, m), 7.13(2H, d, J=7.5Hz), 7.28(2H, d, J=7.5Hz), 7.45(3H, brs), 7.37-8.81(4H, m), 9.93(1H, s), 10.75(1H, s), 12.61(1H, s).

MS: 424(M+H)$^+$ free

Production Example 35: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-phenoxybenzyl)-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[(4-phenoxybenzyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.38(9H, s), 1.51(9H, s), 2.15(3H, s), 2.81-2.97(2H, m), 3.13-3.28(2H, m), 4.35(2H, d, J=5.5Hz), 6.97(4H, d, J=8.5Hz), 7.11(1H, t, J=8.5Hz), 7.13(2H, d, J=8.5Hz), 7.29-7.41(6H, m), 8.54(1H, t, J=5.5Hz), 9.93(1H, s), 11.44(1H, brs), 12.37(1H, brs).

MS: 729(M+H)$^+$

Step 2

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.81-3.00(2H, m), 3.13-3.30(2H, m), 4.35(2H, d, J=5.5Hz), 6.98(4H, d, J=8.5Hz), 7.12(2H, d, J=8.5Hz), 7.13(1H, t, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.40(2H, t, J=8.5Hz), 7.46(3H, brs), 8.67(1H, t, J=5.5Hz), 9.92(1H, s), 12.39(1H, brs).

MS: 529(M+H)$^+$ free

Production Example 36: Synthesis of ethyl 4-({2-(acetylamino)-4-[2-({4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-1-piperazinecarboxylate

Step 1

Ethyl 4-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)carbonyl]-1-piperazinecarboxylate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.17(3H, t, J=7.0Hz), 1.39(9H, brs), 1.50(9H, brs), 2.15(3H, s), 2.90(4H, m), 3.38(8H, brs), 4.03(2H, q, J=7.0Hz), 7.12(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.94(1H, s), 11.46(1H, brs), 12.40(1H, brs).

MS: 688(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 2 of the following Production Example 48.

mp. 180-182.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.18(3H, t, J=7.0Hz), 2.07(3H, s), 2.77(4H, s), 3.43(8H, brs), 4.05(2H, q, J=7.0Hz), 6.89(2H, d, J=7.5Hz), 7.02(2H, d, J=7.5Hz).

MS: 488(M+H)$^+$

Production Example 37: Synthesis of N-{5-[(4-acetyl-1-piperazinyl)carbonyl]-4-[2-({4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-

yl}acetamide

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(4-acetyl-1-piperazinyl)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, brs), 1.50(9H, brs), 1.98(3H, s), 2.15(3H, s), 2.90(4H, m), 3.40(8H, brs), 7.13(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.93(1H, s), 11.43(1H, brs), 12.40(1H, brs).

MS: 658$(M+H)^+$

Step 2

The title compound was prepared in a similar manner according to Step 2 of the following Production Example 48.

mp. 206-207.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.01(3H, s), 2.05(3H, s), 2.73(4H, s), 3.42(8H, brs), 6.77-7.08(4H, m).

MS: 458$(M+H)^+$

Production Example 38: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(methylsulfonyl)-1-piperazinyl]carbonyl}-1,3-thiazol-2-yl)acetamide hydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(methylsulfonyl)-1-piperazinyl]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.89(3H, s), 2.82-2.96(4H, m), 3.01-3.13(4H, m), 3.44-

3.59(4H, m), 7.14(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz), 9.94(1H, s), 11.44(1H, brs), 12.40(1H, brs).

MS: 694(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 118-119°C

^{1}H-NMR (DMSO-d$_6$), δ (ppm): 2.16(3H, s), 2.90(3H, s), 2.83-2.98(4H, m), 3.06-3.18(4H, m), 3.50-3.61(4H, m), 7.12(2H, d, J=8.5Hz), 7.21(2H, d, J=8.5Hz), 7.43(3H, s), 9.90(1H, s), 12.41(1H, s).

MS: 494(M+H)$^+$ free

Production Example 39: Synthesis of N-[4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-(4-thiomorpholinylcarbonyl)-1,3-thiazol-2-yl]acetamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(4-thiomorpholinylcarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d$_6$), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.45-2.61(4H, m), 2.79-2.99(4H, m), 3.55-3.70(4H, m), 7.13(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.92(1H, s), 11.44(1H, brs), 12.38(1H, brs).

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 134-135.5°C

^{1}H-NMR (DMSO-d$_6$), δ (ppm): 2.16(3H, s), 2.47-2.62(4H, m), 2.80-3.00(4H, m), 3.59-3.73(4H, m), 7.12(2H, d, J=8.5Hz), 7.20(2H,

d, J=8.5Hz), 7.39(3H, s), 9.80(1H, s), 12.38(1H, s).

MS: 433(M+H)$^+$ free

Production Example 40: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(1,1-dioxido-4-thiomorpholinyl)carbonyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(1,1-dioxido-4-thiomorpholinyl)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 1 of Production Example 39 in a similar manner according to Step 2 of Production Example 32.

mp. 270-271.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.85-2.96(4H, m), 3.09-3.21(4H, m), 3.69-3.83(4H, m), 7.13(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 9.93(1H, s), 11.47(1H, brs), 12.42(1H, brs).

MS: 665(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 185-186°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.92(4H, s), 3.11-3.28(4H, m), 3.76-3.91(4H, m), 7.12(2H, d, J=8.5Hz), 7.22(2H, d, J=8.5Hz), 7.40(3H, s), 9.84(1H, s), 12.40(1H, s).

MS: 465(M+H)$^+$ free

Production Example 41: Synthesis of ethyl 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-4-piperidinecarboxylate hydrochloride

Step 1

Ethyl 1-{[2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-

butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl]carbonyl}-4-piperidinecarboxylate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.17(3H, t, J=7.0Hz), 1.32-1.56(2H, m), 1.39(9H, s), 1.50(9H, s), 1.73-1.89(2H, m), 2.15(3H, s), 2.44-2.64(1H, m), 2.80-3.01(6H, m), 3.74-3.93(2H, m), 4.06(2H, q, J=7.0Hz), 7.11(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.93(1H, s), 11.45(1H, brs), 12.36(1H, brs).

MS: 687$(M+H)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.18(3H, t, J=7.0Hz), 1.29-1.54(2H, m), 1.73-1.93(2H, m), 2.15(3H, s), 2.44-2.71(1H, m), 2.79-3.09(6H, m), 3.79-3.96(2H, m), 4.09(2H, q, J=7.0Hz), 7.11(2H, d, J=8.5Hz), 7.19(2H, d, J=8.5Hz), 7.40(3H, s), 9.83(1H, s), 12.37(1H, s).

MS: 487$(M+H)^+$ free

Production Example 42: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-4-piperidinecarboxamide hydrochloride

Step 1

Ethyl 1-[(2-(acetylamino)-4-{2-[4-(((Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)carbonyl]-4-piperidinecarboxylate (277.9 mg), 1N-NaOH (1.01 ml) and 1,4-dioxane (3 ml) were combined at 0°C, and the reaction mixture was stirred at r.t. for 3 hours. The mixture was neutrallized with 1N-HCl, and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in*

vacuo to give 1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)carbonyl]-4-piperidinecarboxylic acid (262.4 mg) as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.28-1.59(2H, m), 1.45(18H, s), 1.72-1.90(2H, m), 2.15(3H, s), 2.40-2.59(1H, m), 2.78-3.03(6H, m), 3.77-3.94(2H, m), 7.12(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 9.94(1H, brs), 11.44(1H, brs), 12.36(1H, s).

MS: 659(M+H)$^+$

Step 2

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(aminocarbonyl)-1-piperidinyl]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.29-1.55(2H, m), 1.39(9H, s), 1.50(9H, s), 1.62-1.79(2H, m), 2.14(3H, s), 2.22-2.43(1H, m), 2.78-2.99(6H, m), 3.89-4.07(2H, m), 6.80(1H, s), 7.14(2H, d, J=8.5Hz), 7.27(1H, s), 7.41(2H, d, J=8.5Hz), 9.93(1H, s), 11.44(1H, brs), 12.36(1H, s).

MS: 658(M+H)$^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.27-1.52(2H, m), 1.64-1.79(2H, m), 2.15(3H, s), 2.25-2.44(2H, m), 2.76-3.02(6H, m), 6.82(1H, br), 7.11(2H, d, J=8.5 Hz), 7.19(2H, d, J=8.5 Hz), 7.34(1H, br), 7.41(4H, s), 9.83(1H, s), 12.36(1H, s).

MS: 458(M+H)$^+$ free

Production Example 43: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-N-methyl-4-piperidinecarboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(methylamino)carbonyl]-1-piperidinyl}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 1 of Production Example 42 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.30-1.75(4H, m), 1.39(9H, s), 1.50(9H, s), 2.14(3H, s), 2.22-2.42(1H, m), 2.55(2H, d, J=4.5Hz), 2.78-2.99(6H, m), 3.90-4.03(2H, m), 7.14(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 7.73(1H, q, J=4.5Hz), 9.93(1H, s), 11.43(1H, brs), 12.36(1H, brs).

MS: 672(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.29-1.52(2H, m), 1.60-1.77(2H, m), 2.15(3H, s), 2.55(3H, d, J=4.5 Hz), 2.78-2.98(6H, m), 3.88-4.06(3H, m), 7.11(2H, d, J=8.5 Hz), 7.19(2H, d, J=8.5 Hz), 7.37(4H, br), 7.81(1H, m), 9.75(1H, s), 12.36(1H, s).

MS: 472(M+H)$^+$ free

Production Example 44: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-N,N-dimethyl-4-piperidinecarboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(dimethylamino)carbonyl]-1-piperidinyl}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 1 of Production Example 42 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.30-1.70(4H, m), 1.39(9H, s), 1.50(9H, s), 2.15(3H, s), 2.80(3H, s), 2.79-3.01(7H, m),

3.00(3H, s), 3.88-4.06(2H, m), 7.13(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.92(1H, s), 11.42(1H, brs), 12.36(1H, brs).
MS: 686(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.
^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.27-1.51(2H, m), 1.55-1.72(2H, m), 2.15(3H, s), 2.80(3H, s), 2.81-3.00(6H, m), 3.03(3H, s), 3.89-3.96(3H, m), 7.11(2H, d, J=8.5 Hz), 7.20(2H, d, J=8.5 Hz), 7.37(4H, br), 9.79(1H, s), 12.36(1H, s).
MS: 486(M+H)$^+$

Production Example 45: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-phenyl-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

2-Oxo-3-phenylpropanoic acid (20 g), DMF (100 ml) and DBU (18.2 ml) were combined at 0°C under N_2 atmosphere, and the mixture was stirred at 0°C for an hour. Then iodomethane (15.2 ml) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 3 hours, and poured into 1N-HCl. The mixture was extracted with AcOEt (twice). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / AcOEt (30:1) as an eluent, and triturated with IPE / *n*-Hexane to give methyl 2-oxo-3-phenylpropanoate (11.2 g) as a pale yellow wax.
^{1}H-NMR ($CDCl_3$), δ (ppm): 3.92(3H, s), 6.42(1H, s), 6.53(1H, s), 7.28-7.42(3H, m), 7.77(2H, dd, J=8.5, 1.5Hz).
MS: 179(M+H)$^+$

Step 2

Methyl 2-oxo-3-phenylpropanoate (11 g), pyridinium tribromide (24.1 g), CH_2Cl_2 (490 ml) and AcOH (1.5 ml) were combined at 0°C under N_2 atmosphere. The reaction mixture was

stirred at 0°C for 1.5 hours, poured into water and participated. The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual oil was dissolved in EtOH (190 ml), and then thiourea (6.11 g) was added to the solution. The reaction mixture was refluxed for an hour under N_2 atmosphere. After cooled to 0°C, water was added to the solution. The precipitate was filtered *in vacuo* to give methyl 2-amino-5-phenyl-1,3-thiazole-4-carboxylate (6.63 g) as an off-white solid.

mp. 208-208.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 3.67(3H, s), 7.38-7.53(5H, m).

MS: 235$(M+H)^+$

Step 3

Methyl 2-amino-5-phenyl-1,3-thiazole-4-carboxylate (3 g) was dissolved in pyridine (30 ml), and then acetyl chloride (2.73 ml) was added dropwise to the solution at 0°C under N_2 atmosphere. The reaction mixture was stirred at r.t. for 1.5 hours. Water was added to the solution at 0°C. The precipitate was filtered *in vacuo*, and the solid was washed with ethyl ether to give methyl 2-(acetylamino)-5-phenyl-1,3-thiazole-4-carboxylate (2.37 g) as a pale brown solid.

mp. 224.5-225.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 3.68(3H, s), 7.39-7.57(5H, m), 12.56(1H, s).

MS: 277$(M+H)^+$

Step 4

Methyl 2-(acetylamino)-5-phenyl-1,3-thiazole-4-carboxylate (2.34 g) was suspended in THF (23 ml), and then lithium aluminium hydride (482 mg) was added portionwise to the solution at 0°C. The reaction mixture was stirred at 0°C for 1.5 hours and quenched with MeOH. AcOEt and 1N HCl were added to the mixture, and the mixture was extracted. The aqueous layer was extracted with AcOEt (twice). The combined

organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid was dissolved in MeOH (5 ml) and $CHCl_3$ (90 ml). Then manganase(IV) oxide (11 g) was added to the solution under N_2 atmosphere. The reaction mixture was stirred at r.t. for 13 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / MeOH (20:1) as an eluent to give N-(4-formyl-5-phenyl-1,3-thiazol-2-yl)acetamide (705.2 mg) as a brown amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.19(3H, s), 7.49-7.58(3H, m), 7.60-7.69(2H, m), 9.78(1H, s), 12.60(1H, s).

MS: 247$(M+H)^+$

Step 5

1-(Bromomethyl)-4-nitrobenzene (1.03 g), triphenylphosphine (1.25 g) and DMF (14 ml) were combined under N_2 atmosphere. The reaction mixture was stirred at r.t. for 6 hours. Then potassium tert-butoxide (629 mg) and N-(4-formyl-5-phenyl-1,3-thiazol-2-yl)acetamide (690 mg) were added to the mixture, and the mixture was stirred at r.t. for 13 hours. The reaction mixture was poured into ice-water, and extracted with AcOEt. The organic layer was washed with 1N-HCl, water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / AcOEt (1:1) as an eluent to give a mixture of N-{4-[(E)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide and N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide (E : Z = 2 : 1) (1.02 g) as an orange wax.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3Hx1/3, s), 2.19(3Hx2/3, s), 6.65(1Hx1/3, d, J=12.5Hz), 6.78(1Hx1/3, d, J=12.5Hz), 7.32(1Hx2/3, d, J=15.5Hz), 7.39-7.59(5H+1Hx2/3, m), 7.61(2Hx1/3, d, J=9.0Hz), 7.77(2Hx2/3, d, J=9.0Hz),

8.13(2Hx1/3, d, J=9.0Hz), 8.19(2Hx2/3, d, J=9.0Hz), 12.33(1H, brs).

MS: 366(M+H)$^+$

Step 6

A mixture of N-{4-[(E)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide and N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide (E : Z = 2 : 1) (600 mg), 10% palladium carbon (657 mg), MeOH (6 ml), THF (6 ml) and AcOH (1 ml) were combined. The reaction mixture was stirred under 3 atm H_2 at r.t. for 3.5 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. 1N-NaOH was added to the residue, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give N-{4-[2-(4-aminophenyl)ethyl]-5-phenyl-1,3-thiazol-2-yl}acetamide (528.6mg) as a pale brown amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.80(4H, s), 4.82(2H, s), 6.45(2H, d, J=8.5Hz), 6.78(2H, d, J=8.5Hz), 7.21-7.44(5H, m), 12.18(1H, brs).

MS: 338(M+H)$^+$

Step 7

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-phenyl-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.21(9H, s), 1.44(9H, s), 2.15(3H, s), 2.83-2.98(4H, m), 7.10(2H, d, J=8.5Hz), 7.22-7.47(7H, m), 9.92(1H, s), 11.43(1H, s), 12.22(1H, s).

MS: 580(M+H)$^+$

Step 8

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 80-82°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.83-3.08(4H, m), 7.11(2H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 7.29-7.54(8H, m), 9.94(1H, s), 12.22(1H, brs).

MS: 380(M+H)$^+$ free

Production Example 46: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-benzyl-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

To a suspension of copper(II) bromide (9.75 g) in AcOEt (150 ml) was added a solution of ethyl 2-oxo-4-phenylbutanoate (3 g) in 75 ml of $CHCl_3$. The reaction mixture was refluxed for 23 hours, cooled to r.t., and filtered through a short pad of silica gel eluting with AcOEt / n-hexane (1:1). The solvent was removed *in vacuo* to give ethyl 3-bromo-2-oxo-4-phenylbutanoate (4.2g) as a yellow liquid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.37(3H, t, J=7.0Hz), 3.25(1H, dd, J=14.5, 7.5Hz), 3.54(1H, dd, J=14.5, 7.5Hz), 4.35(2H, q, J=7.0Hz), 5.27(1H, d, J=7.5Hz), 7.18-7.41(5H, m).

Step 2

Ethyl 3-bromo-2-oxo-4-phenylbutanoate (5.8 g) was dissolved in EtOH (110 ml), and then thiourea (3.1 g) was added to the solution. The reaction mixture was refluxed for 2 hours under N_2 atmosphere. The cooled reaction mixture was evaporated *in vacuo*. The residual solid was suspended (pH=8) in saturated $NaHCO_3$ and water. The solid was collected by filtration, and purified by flash column chromatography over silica gel with $CHCl_3$ / MeOH (10:1) as an eluent to give ethyl 2-amino-5-benzyl-1,3-thiazole-4-carboxylate (808.2 mg) as a yellow wax.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.25(3H, t, J=7.0Hz), 4.21(2H, q, J=7.0Hz), 4.33(2H, s), 7.02(2H, s), 7.11-7.39(5H, m).

MS: 263(M+H)$^+$

Step 3

Ethyl 2-(acetylamino)-5-benzyl-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 3 of Production Example 45.

mp. 178-180°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.28(3H, t, J=7.0Hz), 2.09(3H, s), 4.28(2H, q, J=7.0Hz), 4.48(2H, s), 7.19-7.39(5H, m), 12.41(1H, s).

MS: 305$(M+H)^+$

Step 4

Ethyl 2-(acetylamino)-5-benzyl-1,3-thiazole-4-carboxylate (1.0 g) was dissolved in THF(20 ml), and then lithium borohydride (124 mg) was added portionwise to the solution at 0°C. The reaction mixture was refluxed for 4.5 hours and quenched with MeOH. The mixture was concentrated *in vacuo*, and purified by flash column chromatography over silica gel with $CHCl_3$ / MeOH (20:1) as an eluent. The residual amorphous substance was dissolved in MeOH (1 ml) and $CHCl_3$ (8 ml). Then manganase(IV) oxide (1.26 g) was added to the solution under N_2 atmosphere. The reaction mixture was stirred at r.t. for 12 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / MeOH (20:1) as an eluent to give N-(5-benzyl-4-formyl-1,3-thiazol-2-yl)acetamide (251 mg) as a pale yellow solid.

mp. 191-192.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 4.53(2H, s), 7.19-7.40(5H, m), 10.04(1H, s), 12.34(1H, s).

MS: 261$(M+H)^+$

Step 5

N-{5-Benzyl-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

Z : E = 2 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3Hx2/3, s), 2.12(3Hx1/3, s), 4.08(2Hx2/3, s), 4.34(2Hx1/3, s), 6.72(1Hx2/3, d, J=12.5Hz), 6.86(1Hx2/3, d, J=12.5Hz), 7.17-7.39(5H+2Hx1/3, m), 7.66(2Hx2/3, d, J=9.0Hz), 7.92(2Hx1/3, d, J=9.0Hz), 8.14(2Hx2/3, d, J=9.0Hz), 8.22(2Hx1/3, d, J=9.0Hz), 11.85(1Hx2/3, s), 12.16(1Hx1/3, s).

MS: 380(M+H)$^+$

Step 6

N-{4-[2-(4-Aminophenyl)ethyl]-5-benzyl-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 6 of Production Example 45.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.07(3H, s), 2.59-2.85(4H, m), 3.85(2H, s), 4.84(2H, s), 6.46(2H, d, J=8.5Hz), 6.78(2H, d, J=8.5Hz), 7.07(2H, d, J=8.0Hz), 7.16-7.31(3H, m), 11.96(1H, s).

MS: 352(M+H)$^+$

Step 7

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-benzyl-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.07(3H, s), 2.85(4H, s), 3.89(2H, s), 7.05-7.33(7H, m), 7.42(2H, d, J=8.5Hz), 9.95(1H, s), 11.44(1H, s), 11.99(1H, s).

MS: 594(M+H)$^+$

Step 8

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 97-99°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.86(4H, s), 3.93(2H, s), 7.05-7.37(9H, m), 7.47(3H, s), 9.98(1H, s), 12.01(1H, brs).

MS: 394(M+H)$^+$ free

Production Example 47: Synthesis of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

3-(4-Mercaptophenyl)propanoic acid (5 g), K_2CO_3 (11.4 g) and DMF (30 ml) were combined, and iodomethane (5.12 ml) was added dropwise to the mixture at 0°C under N_2 atmosphere. The reaction mixture was stirred at r.t. for 13 hours, and poured into ice-water. The mixture was extracted with AcOEt. The organic layer was washed with water (twice) and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give methyl 3-[4-(methylthio)phenyl]propanoate (4.19 g) as pale yellow oil.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.47(3H, s), 2.61(2H, t, J=8.0Hz), 2.91(2H, t, J=8.0Hz), 3.67(3H, s), 7.12(2H, d, J=8.5Hz), 7.20(2H, d, J=8.5Hz).

Step 2

Sodium methoxide, 28% solution in MeOH (3.67 ml), was added dropwise to the mixture of methyl 3-[4-(methylthio)phenyl]propanoate (4 g) and diethyl oxalate (5.17 ml) at 0°C with stirring. The reaction mixture was stirred at 65°C for 30 minutes under reduced pressure. 15% Aqueous H_2SO_4 (35 ml) was added to the mixture, and the mixture was refluxed for 15 hours. After cooled to r.t., the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual oil was dissolved in EtOH (20 ml), and concentrated H_2SO_4 (0.4 ml) was added dropwise to the solution. The reaction mixture was refluxed for 2 hours. After cooled to r.t., EtOH was removed *in vacuo*. AcOEt and water were added to the residue, and extracted. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column

chromatography over silica gel with *n*-hexane / AcOEt (6:1) as an eluent to give ethyl 4-[4-(methylthio)phenyl]-2-oxobutanoate (2.43 g) as a yellow liquid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.35(3H, t, J=7.0Hz), 2.46(3H, s), 2.92(2H, t, J=7.0Hz), 3.16(2H, t, J=7.0Hz), 4.31(2H, q, J=7.0Hz), 7.13(2H, d, J=8.5Hz), 7.20(2H, d, J=8.5Hz).

Step 3

Ethyl 3-bromo-4-[4-(methylthio)phenyl]-2-oxobutanoate was prepared in a similar manner according to Step 1 of Production Example 46.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.37(3H, t, J=7.0Hz), 2.47(3H, s), 3.20(1H, dd, J=14.5, 7.5Hz), 3.49(1H, dd, J=14.5, 7.5Hz), 4.35(2H, q, J=7.0Hz), 5.22(1H, d, J=7.5Hz), 7.17(2H, d, J=8.5Hz), 7.20(2H, d, J=8.5Hz).

Step 4

Ethyl 2-amino-5-[4-(methylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 2 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.25(3H, t, J=7.0Hz), 2.44(3H, s), 4.20(2H, q, J=7.0Hz), 4.28(2H, s), 7.02(2H, s), 7.19(4H, s).

MS: 309$(M+H)^+$

Step 5

Ethyl 2-(acetylamino)-5-[4-(methylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 3 of Production Example 45.

mp. 205-206°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.28(3H, t, J=7.0Hz), 2.09(3H, s), 2.45(3H, s), 4.27(2H, q, J=7.0Hz), 4.43(2H, s), 7.22(4H, s), 12.41(1H, s).

MS: 351$(M+H)^+$

Step 6

N-{4-Formyl-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to

Step 4 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.45(3H, s), 4.48(2H, s), 7.23(4H, s), 10.03(1H, s), 12.33(1H, s).

MS: 307(M+H)$^+$

Step 7

N-{5-[4-(Methylthio)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

Z : E = 2 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3Hx2/3, s), 2.12(3Hx1/3, s), 2.44(3H, s), 4.04(2Hx2/3, s), 4.30(2Hx1/3, s), 6.71(1Hx2/3, d, J=12.5Hz), 6.84(1Hx2/3, d, J=12.5Hz), 7.18(4Hx2/3, s), 7.23(4Hx1/3, s), 7.24(1Hx1/3, d, J=15.5Hz), 7.40(1Hx1/3, d, J=15.5Hz), 7.65(2Hx2/3, d, J=9.0Hz), 7.92(2Hx1/3, d, J=9.0Hz), 8.12(2Hx2/3, d, J=9.0Hz), 8.22(2Hx1/3, d, J=9.0Hz), 11.85(1Hx2/3, brs), 12.16(1Hx1/3, brs).

MS: 426(M+H)$^+$

Step 8

N-{5-[4-(Methylsulfonyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 2 of Production Example 32.

Z : E = 2 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3Hx2/3, s), 2.13(3Hx1/3, s), 3.18(3H, s), 4.24(2Hx2/3, s), 4.49(2Hx1/3, s), 6.73(1Hx2/3, d, J=12.5Hz), 6.86(1Hx2/3, d, J=12.5Hz), 7.33(1Hx1/3, d, J=15.5Hz), 7.41-7.97(5/3H, m), 7.48(2Hx2/3, d, J=9.0Hz), 7.55(2Hx1/3, d, J=9.0Hz), 7.65(2Hx2/3, d, J=9.0Hz), 7.85(2Hx2/3, d, J=9.0Hz), 8.14(2Hx2/3, d, J=9.0Hz), 8.22(2Hx1/3, d, J=9.0Hz), 11.90(1Hx2/3, s), 12.22(1Hx1/3, s).

MS: 458(M+H)$^+$

Step 9

The title compound was prepared in a similar manner according to Step 6 of Production Example 45.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.58-2.87(4H, m), 3.18(3H, s), 3.98(2H, s), 4.85(2H, s), 6.46(2H, d, J=8.5Hz), 6.77(2H, d, J=8.5Hz), 7.27(2H, d, J=8.5Hz), 7.82(2H, d, J=8.5Hz), 12.02(1H, s).

MS: 430(M+H)$^+$

Production Example 48: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Example 47 in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.08(3H, s), 2.86(4H, s), 3.16(3H, s), 4.03(2H, s), 7.13(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 7.81(2H, d, J=8.5Hz), 9.97(1H, s), 11.45(1H, s), 12.05(1H, s).

MS: 672(M+H)$^+$

Step 2

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate (953 mg) and 4N HCl in 1,4-dioxane solution (10 ml) were combined under N_2 atmosphere. The reaction mixture was stirred at r.t. for 7 hours. The solvent was removed *in vacuo*. The residue was dissolved in water and AcOEt. The solution was made basic (pH=8) by saturated $NaHCO_3$. The precipitate was filtered *in vacuo* to give N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (667.7 mg) as a pale yellow solid.

mp. 228-229.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.79(4H, m), 3.18(3H, s), 4.05(2H, s), 6.72(2H, d, J=8.0Hz), 6.99(2H, d, J=8.0Hz), 7.37(2H, d, J=8.5Hz), 7.84(2H, d, J=8.5Hz).

MS: 472(M+H)$^+$

Production Example 49: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide hydrochloride

The title compound was prepared from the compound obtained in Step 1 of Production Example 48 in a similar manner according to Step 4 of Production Example 31.

mp. 107-110°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.87(4H, s), 3.19(3H, s), 4.08(2H, s), 7.13(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 7.44(3H, s), 7.85(2H, d, J=8.5Hz), 9.94(1H, s), 12.05(1H, brs).

MS: 472(M+H)$^+$ free

Production Example 50: Synthesis of N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

To a ice-cold solution of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (247.6 mg) in acetone (4.8 ml) was added benzoyl isothiocyanate (94.1 mg), and the mixture was stirred at r.t. for 1 hour. Water was added to the mixture, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual amorphous substance was dissolved in EtOH (5 ml), and 6N-NaOH (0.288 ml) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 2 hours, and neutralized with 1N-HCl at 0°C. The mixture was extracted with AcOEt. The organic layer was washed with water and brine,

dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was solidified with ethyl ether to give N-{4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (290.7 mg) as an off-white solid.

mp. 102-103°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.85(4H, s), 3.18(3H, s), 4.03(2H, s), 7.11(2H, d, J=8.5Hz), 7.30(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.84(2H, d, J=8.5Hz), 9.64(1H, s), 12.04(1H, s).

MS: 489(M+H)$^+$

Step 2

A mixture of N-{4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (281.8 mg), methyl iodide (0.0431 ml) and MeOH (3 ml) was refluxed for 3.5 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with AcOEt and stirred for 30 minutes. The precipitated crystals were filtered and washed with AcOEt to give methyl N-[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]imidothiocarbamate hydroiodide (291.5 mg) as an off-white amorphous solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.68(3H, s), 2.90(4H, s), 3.18(3H, s), 4.07(2H, s), 7.22(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.39(2H, d, J=8.5Hz), 7.86(2H, d, J=8.5Hz), 9.22(1H, brs), 11.11(1H, brs), 12.03(1H, s).

MS: 503(M+H)$^+$ free

Step 3

The title compound was prepared in a similar manner according to the following Production Example 58.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.87(4H, s), 3.19(3H, s), 4.08(2H, s), 7.12(2H, d, J=8.5Hz), 7.23(2H, d, J=8.5Hz),

7.41(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz), 8.92(2H, brs), 12.03(1H, brs).

MS: 487 $(M+H)^+$

Production Example 51: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(ethylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

Ethyl 3-[4-(ethylthio)phenyl]propanoate was prepared from 4-(2-carboxyethyl)thiophenol in a similar manner according to Step 1 of Production Example 47.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.23(3H, t, J=7.0Hz), 1.29(3H, t, J=7.0Hz), 2.60(2H, t, J=8.5Hz), 2.82-2.99(4H, m), 4.12(2H, q, J=7.0Hz), 7.12(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz).

Step 2

Ethyl 4-[4-(ethylthio)phenyl]-2-oxobutanoate was prepared in a similar manner according to Step 2 of Production Example 47.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.31(3H, t, J=7.0Hz), 1.36(3H, t, J=7.0Hz), 2.92(2H, q, J=7.0Hz), 2.93(2H, t, J=7.0Hz), 3.16(2H, t, J=7.0Hz), 4.27(2H, q, J=7.0Hz), 7.08(2H, d, J=9.0Hz), 7.26(2H, d, J=9.0Hz).

Step 3

Ethyl 3-bromo-4-[4-(ethylthio)phenyl]-2-oxobutanoate was prepared in a similar manner according to Step 1 of Production Example 46.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.31(3H, t, J=7.5Hz), 1.38(3H, t, J=7.5Hz), 2.93(2H, q, J=7.5Hz), 3.21(1H, dd, J=14.5, 7.5Hz), 3.49(1H, dd, J=14.5, 7.5Hz), 4.35(2H, q, J=7.5Hz), 5.23(1H, t, J=7.5Hz), 7.16(2H, d, J=8.5Hz), 7.27(2H, d, J=8.5Hz).

Step 4

Ethyl 2-amino-5-[4-(ethylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step

2 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.22(6H, t, J=7.0Hz), 2.94(2H, q, J=7.0Hz), 4.20(2H, q, J=7.0Hz), 4.29(2H, s), 7.03(2H, s), 7.18(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz).

MS: 323$(M+H)^+$

Step 5

Ethyl 2-(acetylamino)-5-[4-(ethylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 3 of Production Example 45.

mp. 189.5-190°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.21(3H, t, J=7.5Hz), 1.28(3H, t, J=7.0Hz), 2.09(3H, s), 2.95(2H, q, J=7.5Hz), 4.27(2H, q, J=7.0Hz), 4.44(2H, s), 7.22(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 12.42(1H, s).

MS: 365$(M+H)^+$

Step 6

N-{5-[4-(Ethylthio)benzyl]-4-formyl-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 4 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.21(3H, t, J=7.5Hz), 2.17(3H, s), 2.95(2H, q, J=7.5Hz), 4.49(2H, s), 7.26(4H, s), 10.03(1H, s), 12.34(1H, s).

Step 7

N-{5-[4-(Ethylthio)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

Z : E = 3 : 2

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.20(3H, t, J=7.5Hz), 2.08(3Hx3/5, s), 2.12(3Hx2/5, s), 2.93(2H, q, J=7.5Hz), 4.05(2Hx3/5, s), 4.31(2Hx2/5, s), 6.71(1Hx3/5, d, J=12.5Hz), 6.84(1Hx3/5, d, J=12.5Hz), 7.13-8.16(6H+4/5H, m), 8.12(2Hx3/5, d, J=9.0Hz), 8.22(2Hx2/5, d, J=9.0Hz), 11.86(1Hx3/5, brs), 12.18(1Hx2/5, brs).

MS: 440 $(M+H)^+$

Step 8

N-{5-[4-(Ethylsulfonyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 2 of Production Example 32.

Z : E = 3 : 2

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.06(3H, t, J=7.5Hz), 2.09(3Hx3/5, s), 2.13(3Hx2/5, s), 3.25(2H, q, J=7.5Hz), 4.24(2Hx3/5, s), 4.50(2Hx2/5, s), 6.73(1Hx3/5, d, J=12.5Hz), 6.87(1Hx3/5, d, J=12.5Hz), 7.43-8.31(8H+4/5H, m), 11.91(1Hx3/5, brs), 12.22(1Hx2/5, brs).

MS: 472 $(M+H)^+$

Step 9

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(ethylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.05(3H, t, J=7.5Hz), 1.39(9H, s), 1.51(9H, s), 2.09(3H, s), 2.85(4H, s), 3.22(2H, q, J=7.5Hz), 4.04(2H, s), 7.11(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 7.77(2H, d, J=8.5Hz), 9.97(1H, s), 11.44(1H, s), 12.05(1H, s).

MS: 686 $(M+H)^+$

Step 10

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.07(3H, t, J=7.5Hz), 2.09(3H, s), 2.86(4H, s), 3.26(2H, q, J=7.5Hz), 4.09(2H, s), 7.13(2H, d, J=8.0Hz), 7.24(2H, d, J=8.0Hz), 7.44(3H, brs), 7.60(2H, d, J=8.0Hz), 7.81(2H, d, J=8.0Hz), 9.89(1H, s), 12.05(1H, brs).

MS: 486 $(M+H)^+$ free

Production Example 52: Synthesis of ethyl {4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-

(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate

Step 1

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (300 mg) was dissolved in THF (3 ml) under N_2 atmosphere. Then di(tert-butyl)dicarbonate (168 mg) in THF (3 ml) was added to the solution at r.t. The reaction mixture was stirred at r.t. for 14 hours, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / AcOEt (1:1) as an eluent to give tert-butyl [4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)-benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (248.5 mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.47(9H, s), 2.08(3H, s), 2.82(4H, s), 3.16(3H, s), 3.99(2H, s), 7.00(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz), 9.24(1H, s), 12.03(1H, s).

MS: 530 $(M+H)^+$

Step 2

tert-Butyl [4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]-carbamate (230 mg), 1N-NaOH (1.09 ml) and EtOH (5 ml) were combined, and the mixture was refluxed for 16 hours. After cooled to r.t., the organic solvent was removed *in vacuo*. The aqueous solution was neutrallized with 1N-HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with $CHCl_3$ / MeOH (30:1) as an eluent to give tert-butyl [4-(2-{2-amino-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (151.2 mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.47(9H, s), 2.58-2.82(4H, m),

3.16(3H, s), 3.84(2H, s), 6.73(2H, s), 7.02(2H, d, J=8.5Hz), 7.21(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.77(2H, d, J=8.5Hz), 9.24(1H, s).

MS: 488(M+H)$^+$

Step 3

tert-Butyl [4-(2-{2-amino-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (140 mg) was dissolved in pyridine (2 ml) under N_2 atmosphere. Then, ethyl chloroformate (30.2 ml) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 2 hours, and concentrated *in vacuo*. The residue was dissolved in AcOEt, and washed with 1N-HCl, water and brine. The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give ethyl {4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate (155.8 mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.21(3H, t, J=7.0Hz), 1.47(9H, s), 2.79(4H, s), 3.16(3H, s), 3.97(2H, s), 4.14(2H, q, J=7.0Hz), 7.00(2H, d, J=8.5Hz), 7.24(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz), 9.54(1H, s), 11.64(1H, brs).

MS: 560(M+H)$^+$

Step 4

Ethyl {4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate (140 mg) and 4N HCl in 1,4-dioxane solution (3 ml) were combined under N_2 atmosphere. The reaction mixture was stirred at r.t. for 2 hours. The solvent was removed *in vacuo*. The residue was dissolved in water and AcOEt. The mixture was made basic (pH=8) by 1N-NaOH. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give ethyl {4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate (125.6mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.21(3H, t, J=7.0Hz), 2.60-2.80(4H, m), 3.18(3H, s), 3.97(2H, s), 4.14(2H, q, J=7.0Hz), 4.85(2H, brs), 6.46(2H, d, J=8.5Hz), 6.77(2H, d, J=8.5Hz), 7.29(2H, d, J=8.5Hz), 7.82(2H, d, J=8.5Hz), 11.62(1H, brs).

MS: 460(M+H)$^+$

Step 5

Di-tert-butyl ((Z)-{[4-(2-{2-[(ethoxycarbonyl)amino]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.21(3H, t, J=7.0Hz), 1.39(9H, s), 1.51(9H, s), 2.84(4H, s), 3.16(3H, s), 4.01(2H, s), 4.14(2H, q, J=7.0Hz), 7.13(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 7.81(2H, d, J=8.5Hz), 9.97(1H, s), 11.45(1H, s), 11.61(1H, brs).

MS: 702(M+H)+

Step 6

The title compound was prepared in a similar manner according to Step 2 of Production Example 48.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.17(3H, t, J=7.0Hz), 2.57(4H, s), 3.17(3H, s), 4.01(2H, q, J=7.0Hz), 4.03(2H, s), 7.00(4H, s), 7.42(2H, d, J=8.5Hz), 7.83(2H, d, J=8.5Hz).

MS: 502(M+H)$^+$

Production Example 53: Synthesis of N-{4-{2-[4-(aminomethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

[4-(Methoxycarbonyl)benzyl](triphenyl)phosphonium bromide (4.81 g) and DMF (60 ml) were combined under N_2 atmosphere. Then potassium tert-butoxide (1.32 g) and N-{4-formyl-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide (3 g) were added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 18 hours, poured into ice-water, and

extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / AcOEt (2:1) as an eluent. The solid was suspended in AcOEt, and the suspension was filtered. The filtrate was concentrated *in vacuo* to give methyl 4-((Z)-2-{2-(acetylamino)-5-[4-(methylthio)benzyl]-1,3-thiazol-4-yl}vinyl)benzoate (4.16 g) as a yellow amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.43(3H, s), 3.84(3H, s), 3.96(2H, s), 6.67(1H, d, J=12.5Hz), 6.74(1H, d, J=12.5Hz), 7.11(2H, d, J=8.5Hz), 7.17(2H, d, J=8.5Hz), 7.50(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz), 11.88(1H, s).

MS: 439(M+H)$^+$

Step 2

Methyl 4-((Z)-2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}vinyl)benzoate was prepared in a similar manner according to Step 2 of Production Example 32.

Z : E = 2 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3Hx2/3, s), 2.12(3Hx1/3, s), 3.18(3H, s), 3.84(3Hx2/3, s), 3.86(3Hx1/3, s), 4.15(2Hx2/3, s), 4.47(2Hx1/3, s), 6.68(1Hx2/3, d, J=12.5Hz), 6.77(1Hx2/3, d, J=12.5Hz), 7.30(1Hx1/3, d, J=15.5Hz), 7.43(2H, d, J=8.5Hz), 7.50-7.97(19/3H, m), 11.93(1Hx2/3, s), 12.19(1Hx1/3, s).

MS: 471(M+H)$^+$

Step 3

Methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

mp. 209-210°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.94(4H, m), 3.17(3H, s), 3.84(3H, s), 4.01(2H, s), 7.25(2H, d, J=8.5Hz), 7.28(2H,

d, J=8.5Hz), 7.76(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz), 12.05(1H, brs).

MS: 473(M+H)$^+$

Step 4

To a stirred solution of methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)benzoate (2 g) in dry THF (40 ml) was added dropwise 1.0M diisobutylaluminium hydride solution in toluene (14.8 ml) at -78°C under N_2 atmosphere. The reaction mixture was stirred at r.t. for 4 hours, and then quenched with MeOH. AcOEt and 1N-HCl were added to the mixture, and extracted. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with $CHCl_3$ / MeOH (20:1) as an eluent to give N-{4-{2-[4-(hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (552.3 mg) as a colorless solid.

mp. 209.5-211°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.86(4H, s), 3.17(3H, s), 4.01(2H, s), 4.46(2H, d, J=5.5Hz), 5.12(1H, t, J=5.5Hz), 7.09(2H, d, J=8.0Hz), 7.20(2H, d, J=8.0Hz), 7.28(2H, d, J=8.5Hz), 7.80(2H, d, J=8.5Hz), 12.04(1H, brs).

MS: 445(M+H)$^+$

Step 5

N-{4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (539.5 mg), CH_2Cl_2 (5 ml) and DMF (5 ml) were combined under N_2 atmosphere. Then, Et_3N (0.211 ml) and MsCl (0.108 ml) were added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 3.5 hours. The reaction mixture was poured into water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give N-{4-{2-[4-

(chloromethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (537.5 mg) as an off-white solid.

mp. 202-203°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.88(4H, s), 3.17(3H, s), 4.01(2H, s), 4.73(2H, s), 7.15(2H, d, J=8.0Hz), 7.30(2H, d, J=8.5Hz), 7.34(2H, d, J=8.0Hz), 7.81(2H, d, J=8.5Hz), 12.05(1H, brs).

MS: 463(M+H)$^+$

Step 6

N-{4-{2-[4-(Chloromethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (150 mg) was suspended in CH_3CN (6 ml), and then 28% ammonia solution (0.4 ml) was added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 16 hours, and concentrated *in vacuo*. The residual solid was washed with water, and purified by preparative silica gel chromatography with $CHCl_3$ / MeOH (10:1) as an eluent to give N-{4-{2-[4-(aminomethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (32.1mg) as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.85(4H, s), 3.17(3H, s), 3.69(2H, s), 4.01(2H, s), 7.07(2H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 7.29(2H, d, J=8.5Hz), 7.80(2H, d, J=8.5Hz).

MS: 444(M+H)+

Production Example 54: Synthesis of N-{4-{2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

A mixture of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}-acetamide (200 mg), 2-(methylsulfanyl)-4,5-dihydro-1,3-thiazole (62 mg), concentrated HCl (0.064 ml) and 2-methoxyethanol (3 ml) was stirred at 120°C for 13 hours under N_2 atmosphere. After cooled to r.t., the reaction mixture was made basic with

saturated $NaHCO_3$. The mixture was extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with $CHCl_3$ / MeOH (10:1) as an eluent to give N-{4-{2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (139.8 mg) as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.82(4H, s), 3.16(3H, s), 3.17-3.34(4H, m), 3.98(2H, s), 6.99(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.45(2H, brd, J=8.5Hz), 7.80(2H, d, J=8.5Hz), 9.24(1H, brs), 12.04(1H, s).

MS: 515$(M+H)^+$

Production Example 55: Synthesis of N-{4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

A mixture of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (150 mg), ethyl 2-(methylthio)-4,5-dihydro-1H-imidazole-1-carboxylate (78.9 mg), AcOH (0.3 ml) and EtOH (3 ml) was refluxed for 7 hours under N_2 atmosphere. After cooled to r.t., the reaction mixture was made basic with saturated $NaHCO_3$. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with $CHCl_3$ / MeOH (10:1) as an eluent. The amorphous substance was solidified with ethyl ether to give N-{4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (17.9 mg) as an off-white amorphous solid.

mp. 139-140°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.71-2.87(4H, m), 3.18(3H, s), 3.25-3.41(4H, m), 4.03(2H, s), 6.95(4H, s), 7.32(2H, d, J=8.5Hz), 7.82(2H, d, J=8.5Hz).

MS: 498(M+H)$^+$

Production Example 56: Synthesis of N-{4-{2-[4-(ethanimidoylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (200 mg), methyl ethanimidothioate hydroiodide (202 mg) and MeOH (4 ml) were combined under N_2 atmosphere. The reaction mixture was refluxed for 3 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residue was purified by preparative NH silica gel chromatography with $CHCl_3$ / MeOH (10:1) as an eluent. The amorphous substance was solidified with ethyl ether to give N-{4-{2-[4-(ethanimidoylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (102.4 mg) as a pale yellow amorphous solid.

mp. 81.5-83°C

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.83(3H, brs), 2.08(3H, s), 2.81(4H, m), 3.18(3H, s), 4.02(2H, s), 6.64(2H, brd, J=8.5Hz), 6.99(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.83(2H, d, J=8.5Hz), 12.03(1H, brs).

MS: 471(M+H)$^+$

Production Example 57: Synthesis of N-[4-(2-{4-[(iminomethyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide

N-{4-[2-(4-Aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (150 mg) was dissolved in THF (2 ml) and pH=7 buffer (2 ml). Then, ethyl imidoformate hydrochloride (1.26 g) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 2 hours, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with CH_3CN / water (7:3) as an eluent. The oil was purified again by preparative silica gel chromatography with $CHCl_3$ / MeOH (5:1) as an eluent to give N-[4-(2-{4-

[(iminomethyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (110 mg) as pale brown oil.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.81-3.01(4H, m), 6.71(1H, s), 7.09-8.00(7H, m), 12.07(1H, s).

MS: 289$(M+H)^+$

Production Example 58: Synthesis of N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

A mixture of methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydroiodide (100 mg), hydrazine monohydrate (0.0525 ml) and THF (3 ml) was stirred at r.t. for 95 hours. The precipitate was filtered off. The filtrate was concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with $CHCl_3$ / MeOH (10:1) as an eluent to give N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (62.7 mg) as a pale pink solid.

mp: 216.5-218°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.92(4H, m), 6.75(1H, s), 7.12(2H, d, J=8.5Hz), 7.27(2H, d, J=8.5Hz), 8.88(1H, brs), 12.07(1H, brs).

MS: 319$(M+H)^+$

Production Example 59: Synthesis of N-(4-{2-[4-(2-amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

Step 1

N-(4-{2-[4-(Chloromethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide was prepared from N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide in a similar manner according to Step 5 of Production Example 53.

mp. 145-146°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.82-2.99(4H, m), 4.72(2H, s), 6.73(1H, s), 7.20(2H, d, J=8.0Hz), 7.33(2H, d, J=8.0Hz), 12.08(1H, brs).

MS: 295(M+H)$^+$

Step 2

NaCN (115 mg), KI (130 mg) and water (1.8 ml) were combined, and then a solution of N-(4-{2-[4-(chloromethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (230 mg) in DMF (7 ml) was added dropwise to the mixture at 0°C. The reaction mixture was stirred at r.t. for 19 hours, poured into water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give N-(4-{2-[4-(cyanomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (149.1 mg) as a colorless solid.

mp. 160-161°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.82-2.97(4H, m), 3.97(2H, s), 6.73(1H, s), 7.21(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 12.08(1H, brs).

MS: 286(M+H)$^+$

Step 3

N-(4-{2-[4-(Cyanomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (600 mg) was dissolved in MeOH (5 ml) and $CHCl_3$ (5 ml), and then HCl gas was bubbled at 0°C for 5 minutes with stirring. The reaction mixture was stood for 17 hours, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give methyl 2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethanimidoate hydrochloride (632.5 mg) as an off-white solid.

mp. 77-78°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.88(4H, s), 4.92(6H, brs), 6.75(1H, s), 7.10-7.20(4H, m), 12.11(1H, brs).

MS: 318(M+H)$^+$ free

Step 4

Methyl 2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethanimidoate hydrochloride (600 mg) was

dissolved in EtOH (12 ml). Then ammonium chloride (136 mg) and ammonia in methanol (2 ml) were added to the solution. The reaction mixture was refluxed for 4 hours under N_2 atmosphere. After cooled to r.t., the suspension was filtered *in vacuo*. The filtrate was concentrated *in vacuo*, and the residue was solidified with EtOH / diethyl ether to give N-(4-{2-[4-(2-amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (338.6 mg) as an off-white solid.

mp. 190.5-192°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.89(4H, m), 3.68(2H, s), 6.74(1H, s), 7.20(2H, d, J=8.0Hz), 7.39(2H, d, J=8.0Hz).

MS: 303(M+H)$^+$ free

Step 5

N-(4-{2-[4-(2-Amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (67 mg) was dissolved in water (1 ml) and CH_3CN (1 ml). The solution was made basic (pH=8) with saturated $NaHCO_3$, and concentrated *in vacuo*. The residue was purified by preparative NH silica gel chromatography with CH_3CN / water (7:3) as an eluent to give N-(4-{2-[4-(2-amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (26 mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.89(4H, m), 3.59(2H, s), 6.72(1H, s), 7.20(2H, d, J=8.0Hz), 7.30(2H, d, J=8.0Hz), 9.38(3H, brs).

MS: 303(M+H)$^+$

Production Example 60: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

A mixture of N-{5-[4-(methylthio)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-[4-(methylthio)benzyl]-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z : E = 2 : 1) (570 mg) was dissolved

in CH_2Cl_2 (6 ml) under N_2 atmosphere. Then *m*-CPBA (254 mg) was added portionwise to the solution at 0°C. The reaction mixture was stirred at r.t. for 1.5 hours, and diluted in MeOH / $CHCl_3$. The organic solution was washed with 1N-Na_2CO_3, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a mixture of N-{5-[4-(methylsulfinyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-[4-(methylsulfinyl)benzyl]-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z : E = 2 : 1) (282.8 mg) as a yellow amorphous substance.

Z : E = 2 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3Hx2/3, s), 2.13(3Hx1/3, s), 2.71(3H, s), 4.18(2Hx2/3, s), 4.44(2Hx1/3, s), 6.73(1Hx2/3, d, J=12.5Hz), 6.87(1Hx2/3, d, J=12.5Hz), 7.34(1Hx1/3, d, J=15.5Hz), 7.41-8.17(7/3H, m), 7.41(2Hx2/3, d, J=8.0Hz), 7.50(2Hx1/3, d, J=8.0Hz), 7.63(2Hx2/3, d, J=8.0Hz), 7.93(2Hx1/3, d, J=8.0Hz), 8.14(2Hx2/3, d, J=8.0Hz), 8.22(2Hx1/3, d, J=8.0Hz), 11.89(1Hx2/3, s), 12.20(1Hx1/3, s).

MS: 442(M+H)$^+$

Step 2

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfinyl)benzyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 6 of Production Example 45.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.62-2.84(4H, m), 2.70(3H, s), 3.94(2H, s), 4.85(2H, s), 6.46(2H, d, J=8.5Hz), 6.77(2H, d, J=8.5Hz), 7.23(2H, d, J=8.5Hz), 7.58(2H, d, J=8.5Hz), 12.00(1H, s).

MS: 414(M+H)$^+$

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfinyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in

a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.08(3H, s), 2.69(3H, s), 2.86(4H, s), 3.98(2H, s), 7.12(2H, d, J=8.5Hz), 7.26(2H, d, J=8.0Hz), 7.43(2H, d, J=8.5Hz), 7.57(2H, d, J=8.0Hz), 9.95(1H, s), 11.43(1H, s), 12.02(1H, s).

MS: 656(M+H)+

Step 4

The title compound was prepared in a similar manner according to Step 2 of Production Example 48.

mp. 159.5-161°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.07(3H, s), 2.44(3H, s), 2.79(4H, s), 3.86(2H, s), 6.78(2H, d, J=8.5Hz), 7.02(2H, d, J=8.5Hz), 7.04(2H, d, J=8.5Hz), 7.30(2H, d, J=8.5Hz).

MS: 440(M+H)$^+$

Production Example 61: Synthesis of N-{4-[4-(3-{[amino(imino)methyl]amino}propyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

To a solution of methyl 4-{[4-(methylthio)phenyl]acetyl}benzoate (5 g) in dichloromethane (250 ml) were added acetic acid (0.65 ml) and pyridinium bromide perbromide (6.51 g) at 0°C, and the mixture was stirred for 1 h at the same temperarure. The reaction mixture was poured into water (250 ml) and extracted with ethyl acetate (250 ml). The organic layer was washed with water and brine, dried over magnesium sulfate and evapolated. The residue was washed with diisopropylethyl ether and collected by filtration to give methyl 4-{2-bromo[4-(methylthio)phenyl]acetyl}benzoate as an off-white solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.47(3H; s), 3.94(3H, s), 6.33(3H, s), 7.23(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz).

Step 2

Methyl 4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}benzoate was prepared in a similar manner according to Step 2 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.47(3H, s), 3.83(3H, s), 7.08-7.32(4H, m), 7.52(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz).

MS: 357.1 $(M+H)^+$

Step 3

To a solution of methyl 4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}benzoate (100 mg) in tetrahydrofuran (4 ml) was added portionwise lithium aluminium hydride (21.3 mg), and the mixture was stirred for 1 h at 20°C. To the reaction mixture were added ethyl acetate (10 ml) and water (3 ml). The resulting precipitate was removed by filtration, and the filtrate was washed with brine, dried over sodium sulfate and evaporated to give (4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}phenyl)methanol as a yellow solid, that was used as crude in the next reaction.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.46(3H, s), 4.46(2H, d, J=6.0Hz), 5.17(t, 1H, J=5.5Hz), 7.13(d, 2H, J=5.5Hz), 7.17(d, 2H, J=5.5Hz), 7.20(d, 2H, J=8.5Hz), 7.34(d, 2H, J=8.5Hz).

MS: 329.2 $(M+H)^+$

Step 4

To a suspension of (4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}phenyl)methanol (89.3 mg) in dichloromethane (1 ml) were added pyridine (0.11 ml) and acetylchloride (42.5 μl) at 0°C, and the mixture was stirred at the same temperature for 1 hr. To the reaction mixture was added 1N-hydrochloric acid (10 ml), and the mixture was extracted with ethyl acetate (20 ml x 2). The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated to give a crude green solid (77.6 mg). To a solution of the crude green solid in dichloromethane (3 ml) was added 3-chloroperbenzoic acid (80.7 mg) at 0°C, and the mixture was stirred for 2 hr at

20°C. To the reaction mixture was added saturated sodium hydrogencarbonate aqueous solution (10 ml), and the mixture was extracted with ethyl acetate (20 ml x 2), washed with water and brine, dried over magnesium sulfate, and evaporated to give 4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}benzyl acetate as a brown solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.77(3H, s), 2.14(3H, s), 3.10(3H, s), 5.12(2H, s), 7.32(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz), 7.52(2H, d, J=8.5Hz), 7.88(2H, d, J=8.5Hz), 11.1(1H, brs).

MS: 467.0$(M+Na)^+$

Step 5

To a suspension of 4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}benzyl acetate (1.218 g) in metanol (24 ml) was added potassium carbonate (379 mg) at 20°C, and the mixture was stirred for 1 h. To the reaction mixture was added 0.1N-hydrochloric acid (27.4 ml), and the mixture was extracted with chloroform (500 ml), dried over magnesium sulfate and evaporated to give N-{4-[4-(hydroxymethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.87(3H, s), 3.09(3H, s), 4.72(2H, s), 7.31(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz), 7.51(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 10.83(1H, brs).

MS: 425.0$(M+Na)^+$

Step 6

To a solution of N-{4-[4-(hydroxymethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (867.4 mg) in methanol (0.6 ml) and chloroform (10 ml) was added manganese(IV) oxide (6.65 g) at 20°C under N_2 atmosphere, and the mixture was stirred for 19 hrs. The reaction mixture was filtered through a celite pad. The filtrate was evaporeted to give N-{4-(4-formylphenyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow solid, that was used as

crude in the next reaction.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.20(3H, s), 3.26(3H, s), 7.63(2H, d, J=8.5Hz), 7.64(2H, d, J=8.0Hz), 7.90(2H, d, J=8.0Hz), 7.92(2H, d, J=8.5Hz), 10.00(1H, s), 12.5(1H, brs).

Step 7

To a suspension of N-{4-(4-formylphenyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (360 mg) in chloroform (7 ml) was added (carbethoxymethylene)triphenylphosphorane (626 mg) at 20°C, and the mixture was stirred for 1 h. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel (150 ml) with hexane / ethyl acetate (1:1-1:2) as an eluent to give ethyl (2E)-3-(4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}phenyl)acrylate as a pale yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.34(3H, t, J=7.0Hz), 1.93(3H, s), 3.10(3H, s), 4.28(2H, q, J=7.0Hz), 6.45(1H, d, J=16.1Hz), 7.48(4H, s), 7.54(2H, d, J=8.5Hz), 7.67(2H, d, J=16.1Hz), 7.89(2H, d, J=8.5Hz), 10.39(1H, s).

MS: 493.1(M+Na)+

Step 8

To a suspension of ethyl (2E)-3-(4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}phenyl)acrylate (306.5 mg) in tetrahydrofuran (3 ml) was added portionwise lithium borohydride (271 mg) at 0°C, and the mixture was stirred for 6.5 h at 20°C. The reaction mixture was poured into a mixture of saturated ammonium chloride aqueous solution (50 ml) and chloroform (50 ml) at 0°C. The organic layer was separeted, dried over maganesium sulfate and evaporarted to give a crude yellow solid (300 mg). The residue was purified by column chromatography over silica gel (80 ml) with hexane / ethyl acetate (1:2-1:5) as an eluent to give N-{4-[4-(3-hydroxypropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-

thiazol-2-yl}acetamide as a pale yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.71(3H, s), 1.80-1.99(2H, m), 2.61-2.82(2H, m), 3.09(3H, s), 3.69(2H, dd, J=6.0, 10.0Hz), 7.17(2H, d, J=8.0Hz), 7.37(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 11.1(1H, s).

MS: 431.20(M+1)$^+$

Step 9

To a solution of N-{4-[4-(3-hydroxypropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (75 mg) in tetrahydrofuran (0.7 ml) were added triphenylphosphine (68.5 mg) and carbon tetrabromide (86.7 mg) at 0°C, and the mixture was stirred for 1 h at 20°C. The reaction mixture was purified by preparative thin-layer chromatography over silica gel with hexane / ethyl acetate (1:2) as an eluent to give N-{4-[4-(3-bromopropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as colorless oil.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.67(3H, s), 2.08-2.28(2H, m), 2.80(2H, t, J=7.5Hz), 3.10(3H, s), 3.41(2H, t, J=6.5Hz), 7.18(2H, d, J=8.0Hz), 7.39(2H, d, J=8.0Hz), 7.53(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 11.1(1H, s).

MS: 515.0(M+Na)+

Step 10

To a solution of N-{4-[4-(3-bromopropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (82 mg) in N,N-dimethylformamide (0.82 ml) was added phthalimide potassium salt (30.8 mg), and the mixture was stirred for 2hrs. at 50°C. The reaction mixture was cooled to 20°C, then water was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated to give a crude material (92.0 mg). The crude material was purified by preparative thin-layer chromatography over silica gel to give N-{4-{4-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]phenyl}-5-[4-

(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.72(3H, s), 1.90-2.13(2H, m), 2.60-2.79(2H, m), 3.09(3H, s), 3.74(2H, t, J=7.3Hz), 7.18(2H, d, J=8.0Hz), 7.37(2H, d, J=8.0Hz), 7.52(2H, d, J=8.5Hz), 7.66-7.78(2H, m), 7.80-7.92(4H, m), 11.0(1H, s).

MS: 582.1$(M+Na)^+$

Step 11

To a solution of N-{4-{4-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]phenyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (53.2 mg) in acetonitrile (0.5 ml) was added hydrazine monohydrate (46.1 μl), and the mixture was stirred at 50°C for 30 min. The volatiles were evaporated. To the mixture was added chloroform (1 ml), and an insoluble material was removed by filtration. The filtrate was purified by preparative thin-layer chromatography over NH silica gel with chloroform / methanol (10:1) as an eluent to give N-{4-[4-(3-aminopropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.69(3H, s), 1.69-1.88(2H, m), 2.60-2.74(2H, m), 2.76(2H, t, J=7.0Hz), 3.09(3H, s), 7.15(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.86(2H, d, J=8.5Hz).

MS: 428.2$(M-H)^-$

Step 12

Di-tert-butyl ((E)-{[3-(4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}phenyl)propyl]amino}methylidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.50(9H, s), 1.87-1.97(2H, m), 2.01(3H, s), 2.69(2H, t, J=8.1Hz), 3.09(3H, s), 3.41-3.54(2H, m), 7.16(2H, d, J=8.1Hz), 7.36(2H, d, J=8.1Hz), 7.54(2H, d, J=8.5Hz), 7.87(2H, d, J=8.4Hz), 8.38(1H, t,

J=5.1Hz), 9.87(1H, brs), 11.5(1H, s).

MS: 694.2(M+Na)$^+$

Step 13

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.72-1.85(2H, m), 2.19(3H, s), 2.58-2.66(2H, m), 3.08-3.18(2H, m), 3.25(3H, s), 6.65-7.58(4H, brs), 7.21(2H, d, J=8.4Hz), 7.36(2H, d, J=8.1Hz), 7.56(2H, d, J=8.4Hz), 7.67(1H, t, J=5.1Hz), 7.89(2H, d, J=8.4Hz), 12.4(1H, s).

MS: 472.1(M+H)$^+$ free

Production Example 62: Synthesis of N-{4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide

Step 1

Methyl 4-((E)-2-{2-(acetylamino)-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}vinyl)benzoate was prepared from N-{5-[4-(methylthio)phenyl]-4-formyl-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 53.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3Hx1/3, s), 2.19(3Hx2/3, s), 2.54(3H, s), 3.85(3H, s), 6.55(1Hx1/3, d, J=12.6Hz), 6.73(1Hx1/3, d, J=12.6Hz), 7.17-7.72(8H+2Hx2/3, m), 7.84(2Hx1/3, d, J=8.5Hz), 7.93(2Hx2/3, d, J=8.5Hz), 12.31(1H, brs).

MS: 423.1(M-H)$^-$

Step 2

Methyl 4-((E)-2-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}vinyl)benzoate was prepared in a similar manner according to Step 2 of Production Example 32.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3Hx1/5, s), 2.21(3Hx4/5, s), 3.24(3Hx1/5, s), 3.30(3Hx4/5, s), 3.84(3Hx1/5, s),

3.85(3Hx4/5, s), 6.64(1Hx1/5, d, J=12.6Hz), 6.81(1Hx1/5, d, J=12.6Hz), 7.31(1Hx4/5, d, J=15.6Hz), 7.52(1Hx4/5, d, J=15.6Hz), 7.30-8.11(8H, m), 12.24(1Hx1/5, s), 12.49(1Hx4/5, s).

MS: 479.0(M+Na)$^+$

Step 3

Methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}ethyl)benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

^{1}H-NMR (DMSO-d$_6$), δ (ppm): 2.31(3H, s), 2.97-3.07(4H, m), 3.08(3H, s), 3.91(3H, s), 7.09(2H, d, J=8.1Hz), 7.32(2H, d, J=8.1Hz), 7.87(4H, d, J=8.1Hz), 8.75(1H, s).

MS: 481.0(M+Na)$^+$

Step 4

N-{4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 4 of Production Example 53.

^{1}H-NMR (DMSO-d$_6$), δ (ppm): 2.17(3H, s), 2.96(4H, s), 3.24(3H, s), 4.43(2H, s), 7.06(2H, d, J=8.1Hz), 7.18(2H, d, J=8.1Hz), 7.50(2H, d, J=8.4Hz), 7.91(2H, d, J=8.4Hz), 12.33(1H, s).

MS: 453.1(M+Na)$^+$

Step 5

N-{4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (100 mg), N-hydroxyphthalimide (39.8 mg), triphenylphosphine (64 mg) and tetrahydrofuran (2 ml) were combined under nitrogen atmosphere, then, diethyl azodicarboxylate (40 wt% solution in toluene) (0.111 ml) was added to the solution at 0°C, and the mixture was stirred at 20°C for 5 hrs. The reaction mixture was poured into saturated sodium hydrogen carbonate aqueous solution, and extracted with chloroform. The organic layer was

washed with brine, dried over magnesium sulfate, filtered and evaporated. The crude material was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (30:1) as an eluent to give N-{4-[2-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl}phenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow foam.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.30(3H, s), 2.95-3.00(4H, m), 3.09(3H, s), 5.15(2H, s), 7.04(2H, d, J=8.1Hz), 7.21-7.92(10H, m), 9.31(1H, brs).

MS: 598.1$(M+Na)^+$, 574.0$(M-H)^-$

Step 6

To a solution of N-{4-[2-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl}phenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (116.8 mg) in N,N-dimethylformamide (1.1 ml) was added methylhydrazine (11.9 μl) under N_2 atmosphere, and the mixture was stirred at 20°C for 4hrs. The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added to the residue, and the precipitate was filtered off. The filtrate was concentrated *in vacuo* to give a crude yellow solid (105.1 mg). The crude material was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (30:1) as an eluent to give a pale yellow powder. The obtained powder was washed with acetonitrile, and the precipitate was collected by filtration to give N-{4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (8.4 mg) as a white solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.91-3.02(4H, m), 3.24(3H, s), 4.51(2H, s), 5.98(2H, s), 7.09(2H, d, J=8.1Hz), 7.19(2H, d, J=8.1Hz), 7.51(2H, d, J=8.4Hz), 7.91(2H, d, J=8.1Hz), 12.33(1H, brs).

MS: 468.0$(M+H)^+$

Production Example 63: Synthesis of N-{4-{2-[4-({[amino(imino)methyl]amino}methyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

N-{4-{2-[4-(Bromomethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared from N-(4-[2-{4-(hydroxymethyl)phenyl}ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl)acetamide in a similar manner according to Step 9 of Production Example 61.
^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.90-3.10(4H, m), 3.23(3H, s), 4.67(2H, s), 7.10(2H, d, J=8.1Hz), 7.31(2H, d, J=8.1Hz), 7.48(2H, d, J=8.4Hz), 7.90(2H, d, J=8.4Hz), 12.33(21H, s).
MS: 491.0(M-H)$^-$

Step 2

To a solution of N-{4-{2-[4-(bromomethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (70 mg) in N,N-dimethylformamide (1 ml) was added diformimide sodium salt (13.5 mg), and the mixture was stirred for 10 min at 20°C. To the reaction mixture was added water, the mixture was extracted with ethyl acetate, washed with water twice, dried over magnesium sulfate, and evaporated to give a crude diformimide compound. The diformimide compound was suspended in conc. hydrocloric acid (200 μl), ethanol (2 ml) and methanol (0.5 ml). The reaction mixture was stirred at 20°C for 3hrs., then at 50°C for 3hrs. The volatails were evaporated. To the residue was added saturated sodium hydrogen carbonate aqueous solution, the mixture was extracted with chloroform, dried over maganesium sulfate and evaporated to give crude N-{4-(2-{4-[aminomethyl]phenyl}ethyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide, that was used as crude in the next reaction.

MS: 428.8(M+H)$^+$

Step 3

Di-tert-butyl ((E)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}ethyl)benzyl]amino}methylidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.48(9H, s), 1.51(9H, s), 2.30(3H, s), 2.98(4H, s), 3.08(3H, s), 4.57(2H, d, J=5.1Hz), 7.04(2H, d, J=8.1Hz), 7.17(2H, d, J=8.1Hz), 7.38(2H, d, J=8.4Hz), 7.91(2H, d, J=8.4Hz), 8.54(1H, t, J=5.1Hz), 8.79(1H, s), 11.53(1H, s).

MS: 672.2(M+H)$^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 2.90-3.05(4H, m), 3.25(3H, s), 4.31(2H, d, J=6.2Hz), 6.65-7.73(4H, brs), 7.14(2H, d, J=8.1Hz), 7.18(2H, d, J=8.1Hz), 7.52(2H, d, J=8.4Hz), 7.93(2H, d, J=8.4Hz), 12.35(1H, s).

MS: 506.0(M-H)$^-$

Production Example 64: Synthesis of methyl 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)benzoate hydrochloride

Step 1

Ethyl 4-(4-iodophenyl)-2-oxobutanoate was prepared from Ethyl 3-(4-iodophenyl)propanoate in a similar manner according to Step 2 of Production Example 47.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.35(3H, t, J=7.0Hz), 2.90(2H, t, J=7.5Hz), 3.15(2H, t, J=7.5Hz), 4.31(2H, q, J=7.0Hz), 6.96(2H, d, J=8.0Hz), 7.61(8.5Hz).

MS: 331.0(M-H)$^-$

Step 2

Ethyl 3-bromo-4-(4-iodophenyl)-2-oxobutanoate was

prepared in a similar manner according to Step 1 of Production Example 46.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.38(3H, t, J=7.0Hz), 3.19(1H, dd, J=7.5, 14.6Hz), 3.47(1H, dd, J=7.5, 14.6Hz), 4.36(2H, q, J=7.0Hz), 5.21(1H, dd, J=7.5, 7.5Hz), 7.00(2H, d, J=8.5Hz), 7.65(2H, d, J=8.5Hz).

MS: 369.2

Step 3

Ethyl 3-bromo-4-(4-iodophenyl)-2-oxobutanoate (1.32 g) was dissolved in ethanol (26 ml), and then, thiourea (244 mg) was added to the solution. The reaction mixture was refluxed for 1 h under nitrogen atmosphere. The cooled reaction mixture was evaporated *in vacuo*. The crude material was triturated with diethyl ether to give ethyl 2-amino-5-(4-iodobenzyl)-1,3-thiazole-4-carboxylate hydrobromide as a pale yellow solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.27(3H, t, J=7.0Hz), 4.28(2H, q, J=7.0Hz), 4.31(2H, s), 7.10(2H, d, J=8.5Hz), 7.69(2H, d, J=8.5Hz).

MS: 389.0$(M+H)^+$, 411.0$(M+Na)^+$

Step 4

Ethyl 2-amino-5-(4-iodobenzyl)-1,3-thiazole-4-carboxylate hydrobromide (1.386 g) was dissolved in dichloromethane (14 ml) under nitrogen atmosphere. Then, pyridine (0.765 ml) and acethyl chloride (0.336 ml) were added dropwise to the solution at 0°C. The reaction mixture was stirred at 20°C for 1 h. The organic solution was washed with 1N-hydrochloric acid, water and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was washed with diisopropyl ether to give ethyl 2-(acetylamino)-5-(4-iodobenzyl)-1,3-thiazole-4-carboxylate as a white solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.27(3H, t, J=7.0Hz), 2.09(3H, s), 4.26(2H, q, J=7.0Hz), 4.43(2H, s), 7.10(2H, d, J=8.0Hz), 7.67(2H, d, J=8.0Hz), 12.44(1H, s).

MS: 431.0 $(M+H)^+$, 453.0 $(M+Na)^+$

Step 5

N-[4-Formyl-5-(4-iodobenzyl)-1,3-thiazol-2-yl]acetamide was prepared in a similar manner according to Step 4 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 4.48(2H, s), 7.11(2H, d, J=8.5Hz), 7.68(2H, d, J=8.5Hz), 10.00(1H, s).

MS: 409.0 $(M+Na)^+$

Step 6

N-{5-(4-Iodobenzyl)-4-[2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.07(3Hx2/3, s), 2.15(3Hx1/3, s), 3.96(2Hx2/3, s), 4.12(2Hx1/3, s), 6.63(1Hx2/3, d, J=12.6Hz), 6.70(1Hx2/3, d, J=12.6Hz), 6.94(2Hx2/3, d, J=8.0Hz), 6.99(2Hx1/3, d, J=8.0Hz), 7.12(1Hx1/3, d, J=15.6Hz), 7.25(1Hx1/3, d, J=15.6Hz), 7.39(2Hx2/3, d, J=9.0Hz), 7.56(2Hx1/3, d, J=8.5Hz), 7.62(2Hx2/3, d, J=8.0Hz), 7.65(2Hx1/3, d, J=8.5Hz), 8.00(2Hx2/3, d, J=8.5Hz), 8.22(2Hx1/3, d, J=8.5Hz), 9.85(1Hx1/3, s), 10.18(1Hx2/3, s).

MS: 528.0 $(M+H)^+$

Step 7

To a solution of a mixture of N-{5-(4-iodobenzyl)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-(4-iodobenzyl)-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z:E=2:1) (558.2 mg) in methanol (2.8 ml) and N,N-dimethylformamide (5.5 ml) were added palladium(II) acetate (49.6 mg), 1,3-bis(diphenylphosphino)propane (109 mg) and triethylamine (308 μl). Carbon monooxide gas was bubbled through the solution for 30 min at 25°C. Then the reaction mixture was stirred for 6 hrs. at 70°C under carbon monooxide atmosphere. The reaction mixture was cooled to 25°C, diluted with ethyl acetete, washed with brine, dried over magnesium

sulfate and evaporated to give a crude yellow foam (645 mg). The crude foam was purified by flash column chromatography over silica gel with toluene / ethyl acetate (2:1-3:2) as an eluent, and triturated with ethyl ether to give a mixture of N-{5-(4-(methoxycarbonyl)benzyl)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-(4-(methoxycarbonyl)benzyl)-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z:E=2:3) as a yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.09(3Hx2/5, s), 2.20(3Hx3/5, s), 3.91(3H, s), 4.10(2Hx2/5, s), 4.25(2Hx3/5, s), 7.27(2Hx2/5, s), 7.14(1Hx3/5, d, J=15.6Hz), 7.25(2Hx2/5, d, J=9.0Hz), 7.29(1Hx3/5, d, J=15.6Hz), 7.31(2Hx3/5, d, J=8.5Hz), 7.38(2Hx2/5, d, J=9.0Hz), 7.57(2Hx3/5, d, J=8.5Hz), 7.97(2Hx2/5, d, J=8.5Hz), 7.99(2Hx2/5, d, J=9.0Hz), 8.00(2Hx3/5, d, J=8.5Hz), 8.20(2Hx3/5, d, J=9.0Hz), 9.55(1Hx3/5, brs), 10.11(1Hx2/5, brs).

MS: 460.1(M+Na)$^+$

Step 8

Methyl 4-({2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl}methyl)benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.20(3H, s), 2.80(4H, s), 3.40-3.67(2H, m), 3.83(2H, s), 3.90(3H, s), 6.57(2H, d, J=8.5Hz), 6.84(2H, d, J=8.5Hz), 7.09(2H, d, J=8.0Hz), 7.91(2H, d, J=8.5Hz), 8.96(1H, brs).

MS: 410.2(M+H)$^+$, 432.2(M+Na)$^+$

Step 9

Methyl 4-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]benzoate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.54(9H, s), 2.20(2H, s),

2.83(4H, s), 3.88(2H, s), 3.89(3H, s), 7.03(2H, d, J=8.5Hz), 7.17(2H, d, J=8.0Hz), 7.44(2H, d, J=8.0Hz), 7.93(2H, d, J=8.5Hz), 9.09(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 652.3 $(M+H)^+$, 652.3 $(M+Na)^+$

Step 10

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.86(4H, s), 3.83(3H, s), 3.96-4.10(2H, m), 7.13(2H, d, J=8.5Hz), 7.24(2H, d, J=9.0Hz), 7.28(2H, d, J=8.5Hz), 7.35(4H, s), 7.89(2H, d, J=8.0Hz), 9.71(1H, s), 12.01(1H, s).

MS: 452.2 $(M+H)^-$ free

Production Example 65: Synthesis of 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N,N-dimethylbenzamide hydrochloride

Step 1

Methyl 4-{[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoate was prepared from the compound obtained in Step 8 of Production Example 64 in a similar manner according to Step 1 of Production Example 52.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.52(9H, s), 2.23(3H, s), 2.81(4H, s), 3.86(2H, s), 3.90(3H, s), 6.93(2H, d, J=8.0Hz), 7.13(2H, d, J=8.5Hz), 7.19(2H, d, J=8.0Hz), 7.91(2H, d, J=8.5Hz), 8.48-9.69(1H, brs).

MS: 510.2 $(M+H)^+$, 532.3 $(M+Na)^+$

Step 2

Methyl 4-{[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoate (287.7 mg), 1N-sodium hydroxide (1.41 ml) and ethanol (2.9 ml) were combined, and the mixture was refluxed for 3 hrs. After cooling to 25°C, the organic solvent was removed *in vacuo*. The aqueous solution was acidified with

1N-hydrochloric acid (pH=4), and the precipitate was filtered *in vacuo* to give 312.5 mg of a pale yellow solid. The solid was dissolved in pyridine (4.3 ml) under nitrogen atmosphere, and then, acethyl chloride (0.12 ml) was added dropwise to the solution at 0°C. The reaction mixture was stirred at 25°C for 3 hrs., and pyridine was removed *in vacuo*. The residue was suspended in water, and acidified with 1N-hydrochloric acid. The precipitate was collected *in vacuo*. The solid was washed with water and diethyl ether to give 4-{[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoic acid as a pale yallow solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.47(9H, s), 2.08(3H, s), 2.70-2.90(4H, m), 3.92(2H, s), 6.99(2H, d, J=8.4Hz), 7.10(2H, d, J=8.0Hz), 7.33(2H, d, J=8.0Hz), 7.81(2H, d, J=8.4Hz), 9.24(1H, s), 12.00(1H, s), 12.84(1H, brs).

MS: 494.4(M-H)$^-$

Step 3

To a solution of 4-{[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoic acid (50 mg) in 0.5 ml of dichloromethane were added methylamine hydrochloride (10.7 mg), 1-hydroxybenzotriazole (20.4 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (55.3 μl), then, the mixture was stirred for 3 hrs. at 25°C. The reaction mixture was diluted with 10 ml of chloroform and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under vaccum. The residue was triturated with ethyl acetate and diisopropylether, and collected by filtration to give tert-butyl {4-[2-(2-(acetylamino)-5-{4-[(dimethylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate as a pale yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.51(9H, s), 2.23(3H, s), 2.83(4H, s), 2.95(3H,s), 3.09(3H, s), 3.82(2H, s), 6.47-6.81(1H, brs),

6.94(2H, d, J=8.1Hz), 7.05(2H, d, J=8.1Hz), 7.18(2H, d, J=8.1Hz), 7.28(2H, d, J=8.1Hz), 8.50-9.09(1H, brs).

MS: 523.3(M+H)$^+$, 545.2(M+Na)$^+$

Step 4

tert-Butyl {4-[2-(2-(acetylamino)-5-{4-[(dimethylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate (39.1 mg) and trifluoroacetic acid (1 ml) were combined at 0°C. The reaction mixture was stirred at 25°C for 2 hrs., and concentrated *in vacuo*. The residue was added to chloroform (20 ml) and 1N-sodium hydroxide (10 ml). The oraganic layer was separated, dried with magnesium sulfate, and evaporated to give yellow oil (33.3 mg). The crude yellow oil, N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (45.8 mg) and tetrahydrofuran (0.5 ml) were combined under nitrogen atmosphere, and the mixture was stirred at 25°C for 34 hrs. To the reaction mixture was added N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (11 mg), and the mixture was stirred at 50°C for 3 hrs. Then, the mixture was concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give di-tert-butyl [(E)-({4-[2-(2-(acetylamino)-5-{4-[(dimethylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate as colorless oil (12.9 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 2.21(3H, s), 2.85(4H, s), 2.96(3H, brs), 3.08(3H, brs), 3.86(2H, s), 7.06(2H, d, J=8.5Hz), 7.14(2H, d, J=8.1Hz), 7.33(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 8.81-9.21(1H, brs), 10.25(1H, s), 11.63(1H, s).

MS: 665.3(M+H)$^+$, 687.2(M+Na)$^+$

Step 5

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.86(4H, s), 2.88(3H, s), 2.96(3H, s), 3.97(2H, s), 7.12(2H, d, J=8.4Hz), 7.16(2H, d, J=8.1Hz), 7.23(2H, d, J=8.4Hz), 7.32(2H, d, J=8.1Hz), 7.34(4H, s), 9.70(1H, s), 12.01(1H, s).

MS: 465.2$(M+H)^+$ free

Production Example 66: Synthesis of 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N-methylbenzamide hydrochloride

Step 1

tert-Butyl {4-[2-(2-(acetylamino)-5-{4-[(methylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from the compound obtained in Step 2 of Production Example 65 in a similar manner according to Step 3 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.52(9H, s), 2.23(3H, s), 2.78-2.89(4H, m), 3.00(3H, d, J=4.8Hz), 3.83(2H, s), 6.20(2H, d, J=4.8Hz), 6.36-6.78(1H, brs), 6.94(2H, d, J=8.4Hz), 7.05(2H, d, J=8.4Hz), 7.18(2H, d, J=8.4Hz), 7.63(2H, d, J=8.4Hz), 8.60-9.09(1H, brs).

MS: 509.2$(M+H)^+$, 531.2$(M+Na)^+$

Step 2

Di-tert-butyl [(E)-({4-[2-(2-(acetylamino)-5-{4-[(methylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.54(9H, s), 2.22(3H, s), 2.83(4H, s), 2.99(3H, d, J=4.8Hz), 3.86(2H, s), 6.16(1H, d, J=4.0Hz), 7.01(2H, d, J=8.4Hz), 7.13(2H, d, J=8.4Hz), 7.42(2H, d, J=8.4Hz), 7.66(2H, d, J=8.4Hz), 8.77-9.10(1H, brs), 10.24(1H, s), 11.62(1H, s).

MS: 651.3$(M+H)^+$, 673.3$(M+Na)^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.76(3H, d, J=4.8Hz), 2.86(4H, s), 3.98(2H, s), 7.13(2H, d, J=8.4Hz), 7.19(2H, d, J=8.1Hz), 7.23(2H, d, J=8.4Hz), 7.30(4H, s), 7.74(2H, d, J=8.1Hz), 8.38(2H, d, J=4.4Hz), 9.62(1H, s), 11.99(1H, s).

MS: 451.3(M+H)$^-$ free

Production Example 67: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(dimethylamino)methyl]-1,3-thiazol-2-yl}acetamide dihydrochloride

Step 1

To a solution of N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (500 mg) in acetic acid (3 ml) were added dimethylamine hydrochloride (169 mg) and paraformaldehyde (62.2 mg), and the mixture was stirred at 100°C (bath temp.) for 2 hrs. The solvent was removed *in vacuo*, and the mixture was adjusted to pH=9 with saturated sodium hydrogen carbonate aqueous solution, extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated. The crude compound was purified by flash column chromatography over silica gel with dichloromethane / methanol (100:1) → (20:1) as an eluent to give N-{5-[(dimethylamino)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.08(3H, s), 2.26(6H, s), 3.47(2H, s), 6.63(1H, d, J=12.6Hz), 6.70(1H, d, J=12.6Hz), 7.43(2H, d, J=9.0Hz), 8.03(2H, d, J=9.0Hz), 10.20(1H, brs).

MS: 347(M+H)$^+$, 369(M+Na)$^+$

Step 2

N-{4-[2-(4-Aminophenyl)ethyl]-5-[(dimethylamino)methyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner

according to Step 6 of Production Example 45.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.19(6H, s), 2.23(3H,s), 2.80(4H, s), 3.30(2H, s), 3.56(2H, s), 6.60(2H, d, J=8.4Hz), 6.91(2H, d, J=8.4Hz), 8.54-8.84(1H, brs).

MS: 317.2$(M-H)^-$

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(dimethylamino)methyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in a similar manner according to Step 7 of Production Example 45.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.21(6H, s), 2.22(3H, s), 2.87(4H, s), 3.36(2H, s), 7.09(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 8.89-9.97(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 561.3$(M+H)^+$, 583.3$(M+Na)^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.66(3H, s), 2.68(3H, s), 2.96(4H, s), 4.37(2H, d, J=4.8Hz), 7.15(2H, d, J=8.4Hz), 7.32(2H, d, J=8.4Hz), 7.51(4H, s), 10.08(1H, s), 10.64(1H, t, J=4.8Hz), 12.33(1H, s).

MS: 361.1$(M+H)^+$

Production Example 68: Synthesis of N-{5-[(4-acetyl-1-piperazinyl)methyl]-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide dihydrochloride

Step 1

N-{5-[(4-Acetyl-1-piperazinyl)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.08(6H, s), 2.34-2.59(4H, m), 3.41-3.53(2H, m), 3.56(2H, s), 3.58-3.69(2H, m), 6.62(1H, d, J=12.6Hz), 6.68(1H, d, J=12.6Hz), 7.45(2H, d, J=8.5Hz), 8.05(2H, d, J=9.0Hz), 10.18(1H, s).

MS: 452.0$(M+Na)^+$

Step 2

N-{5-[(4-Acetyl-1-piperazinyl)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (1080 mg), methanol (2 ml), tetrahydrofuran (2 ml), acetic acid (0.3 ml) and then 10% palladium on carbon (150 mg) were combined under nitrogen atmosphere. The mixture was stirred under 3 atm hydrogen for 3 hrs. at 25°C. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo* to give a crude material (192.3 mg). To the residue was added saturated sodium hydrogen carbonate aqueous solution, and the mixture was extracted with chroloform. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a pink amorphous substance (124.7 mg). The pink amorphous substance (124.7 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (93.6 mg) and tetrahydrofuran (2 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at 25°C for 14 hrs., and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(4-acetyl-1-piperazinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate as colorless oil (121.1 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.06(3H, s), 2.24(3H, s), 2.20-2.32(2H, m), 2.33-2.44(2H, m), 2.74-2.96(4H, m), 3.30-3.45(4H, m), 3.52-3.65(2H, m), 7.04(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz), 8.85-10.17(1H, brs), 10.25(1H, s),

11.63(1H, s).

MS: 644.3(M+H)$^+$, 666.1(M+H)$^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.03(3H, s), 2.16(3H, s), 2.75-3.15(8H, m), 3.16-3.63(4H, m), 4.40(2H, s), 7.15(2H, d, J=8.0Hz), 7.32(2H, d, J=8.0Hz), 7.49(4H, s), 10.07(1H, s), 11.29(1H, brs), 12.33(1H, s)

MS: 444.2(M+H)$^+$ free

Production Example 69: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(methylsulfonyl)-1-piperazinyl]methyl}-1,3-thiazol-2-yl)acetamide dihydrochloride

Step 1

N-{5-{[4-(Methylsulfonyl)-1-piperazinyl]methyl}-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.08(3H, s), 2.54-2.66(4H, m), 2.80(3H, s), 3.19-3.34(4H, m), 3.58(2H, s), 6.61(1H, d, J=12.1Hz), 6.69(1H, d, J=12.1Hz), 7.45(2H, d, J=8.5Hz), 8.04(2H, d, J=8.5Hz), 10.09(1H, s).

MS: 467.2(M+H)$^+$, 488.1(M+Na)$^+$

Step 2

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(methylsulfonyl)-1-piperazinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 2.23(3H, s), 2.41-2.56(4H, m), 2.76(3H, s), 2.80-2.89(4H, m), 3.12-3.27(4H, m), 3.42(2H, s), 7.05(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz),

8.57-9.61(1H, brs), 10.25(1H, s), 11.63(1H, s).

MS: 680.3(M+H)$^-$, 702.2(M+Na)$^-$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.97(4H, s), 3.00(3H, s), 3.05-3.28(4H, m), 3.28-3.48(2H, m), 3.59-3.81(2H, m), 4.35-4.60(2H, brs), 7.16(2H, d, J=8.1Hz), 7.32(2H, d, J=8.1Hz), 7.39(4H, s), 9.84(1H, s), 10.64-10.89(1H, brs), 12.34(1H, s).

MS: 480.1(M+H)$^-$ free

Production Example 70: Synthesis of N-[4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-(4-thiomorpholinylmethyl)-1,3-thiazol-2-yl]acetamide dihydrochloride

Step 1

N-[4-[(Z)-2-(4-Nitrophenyl)vinyl]-5-(4-thiomorpholinylmethyl)-1,3-thiazol-2-yl]acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.08(3H, s), 2.57-2.86(8H, m), 3.53(2H, s), 6.62(1H, d, J=12.6Hz), 6.68(1H, d, J=12.6Hz), 7.43(2H, d, J=9.0Hz), 8.0332(2H, d, J=9.0Hz), 10.16(1H, s).

MS: 405.1(M+H)$^+$, 427.1(M+Na)$^+$

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(4-thiomorpholinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.22(3H, s), 2.63(8H, s), 2.80-2.90(4H, m), 3.39(2H, s), 7.06(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz), 8.82-9.39(1H, brs), 10.24(1H,

s), 11.63(1H, s).

MS: 619.3(M+H)$^+$, 641.2(M+Na)$^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.69-2.87(2H, m), 2.97(4H, s), 3.02-3.19(4H, m), 3.48-3.61(2H, m), 4.42(2H, s), 7.15(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.40(4H, s), 9.86(1H, s), 1051-10.69(1H, brs), 12.34(1H, s).

MS: 419.2(M+H)$^-$ free

Production Example 71: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[2-(dimethylamino)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[2-(dimethylamino)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-{2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.72, 2.85(3H, s), 2.89, 2.98(3H, s), 3.16(4H, m), 4.01(2H, m), 7.07(2H, d, J=8.2 Hz), 7.32(2H, d, J=8.2 Hz), 7.87-7.95(1H, m), 9.21(1H, s), 12.36(1H, s).

MS: 490(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[2-(dimethylamino)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride was prepared in a similar manner according to Step 2 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.85(3H, s), 2.86-2.98(5H, m), 3.22(2H, dd, J=8.9, 5.3 Hz), 4.01(2H, d,

J=5.3 Hz), 7.27(2H, d, J=8.5 Hz), 7.33(2H, d, J=8.5 Hz), 7.94(1H, t, J=5.3 Hz), 10.15(2H, br), 12.38(1H, s).

MS: 390(M+H)$^+$ free

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[2-(dimethylamino)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.85(3H, s), 2.85-2.94(2H, m), 2.97(3H, s), 3.17-3.26(2H, m), 4.00-4.04(2H, m), 7.19(1H, d, J=8.0 Hz), 7.42(2H, d, J=8.0 Hz), 7.88(1H, t, J=5.4 Hz), 9.93(1H, s), 11.43(1H, s), 12.38 (1H, s).

MS: 632(M+H)$^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.84(3H, s), 2.89-2.695(2H, m), 2.98(3H, s), 3.19-3.26(2H, m), 3.99(2H, m), 7.13(2H, d, J=8.0 Hz), 7.28(2H, d, J=8.0 Hz), 7.43(4H, br), 7.97(1H, br), 9.86(1H, s), 12.38(1H, s).

MS: 432(M+H)$^+$ free

Production Example 72: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(dimethylamino)-3-oxopropyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[3-(dimethylamino)-3-oxopropyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of

Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.46(9H, s), 2.14(3H, s), 2.55(2H, m), 2.73-2.94(8H, m), 3.14(2H, dd, J=9.1, 6.1 Hz), 3.37(2H, m), 7.05(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 7.89(1H, m), 9.21(1H, s), 12.33(1H, s).

MS: 504(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[3-(dimethylamino)-3-oxopropyl]-1,3-thiazole-5-carboxamide hydrochloride was prepared in a similar manner according to Step 2 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.15(3H, s), 2.57(2H, m), 2.81(3H, s), 2.84-2.98(5H, m), 3.20(2H, dd, J=8.9, 5.4 Hz), 3.36(2H, dd, J=12.8, 7.1 Hz), 7.26(2H, d, J=8.6 Hz), 7.32(2H, d, J=8.6 Hz), 7.95(1H, t, J=5.4 Hz), 10.04(2H, br), 12.35(1H, br).

MS: 403(M+H)$^+$ free

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(dimethylamino)-3-oxopropyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.50(9H, s), 2.14(3H, s), 2.80(3H, s), 2.81-2.93(2H, m), 2.94(3H, s), 3.13-3.29(6H, m), 3.34-3.43(2H, m), 7.17(2H, d), 7.42(2H, d), 7.89(1H, m), 9.93(1H, s), 11.43(1H, s), 12.34(1H, m).

MS: 646(M+H)$^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.56(2H, m), 2.81(3H, s), 2.87-2.95(5H, m), 3.19(2H, m), 3.34(2H, m), 7.11-7.38(4H, m), 7.43(4H, s), 8.02(1H, m), 8.55(1H, br), 9.88(1H, br), 12.36(1H, s).

MS: 445$(M+H)^+$ free

Production Example 73: Synthesis of 2-(acetylamino)-N-[2-(acetylamino)ethyl]-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[2-(acetylamino)ethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.46(9H, s), 1.79(3H, s), 2.14(3H, s), 2.84(2H, m), 3.16-3.22(6H, m), 7.06(2H, d, J=8.5 Hz), 7.33(2H, d, J=8.5 Hz), 7.99(2H, m), 9.21(1H, s), 12.33(1H, s).

MS: 490$(M+H)^+$

Step 2

2-(Acetylamino)-N-[2-(acetylamino)ethyl]-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxamide hydrochloride was prepared in a similar manner according to Step 2 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.79(3H, s), 2.15(3H, s), 2.90-2.98(2H, dd, J=10.1, 6.6 Hz), 3.14-3.26(6H, m), 7.27(2H, d, J=8.9 Hz), 7.32(2H, d, J=8.9 Hz), 7.97-8.06(2H, m), 10.18(2H, br), 12.35(1H, s).

MS: 390$(M+H)^+$ free

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[2-(acetylamino)ethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 1.79(3H, s), 2.15(3H, s), 2.89(2H, m), 3.18(6H, m), 7.18(2H, d, J=8.0 Hz), 7.42(2H, d, J=8.0 Hz), 7.95(2H, m), 9.93(1H, s), 11.43(1H, s), 12.35(1H, s).

MS: 632 $(M+H)^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.79(9H, s), 2.16(9H, s), 2.91(2H, m), 3.10-3.25(6H, m), 7.14(2H, d, J=8.2 Hz), 7.27(2H, d, J=8.2 Hz), 7.42(4H, br), 7.97(1H, br), 8.08(1H, br), 9.83(1H, s), 12.36(1H, s).

MS: 432 $(M+H)^+$ free

Production Example 74: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-{2-[(methylsulfonyl)amino]ethyl}-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl [4-(2-{2-(acetylamino)-5-[({2-[(methylsulfonyl)amino]ethyl}amino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.79-2.89(5H, m), 3.05-3.32(6H, m), 7.04-7.14(3H, m), 7.33(2H, d, J=8.3 Hz), 8.01(1H, br), 9.20(1H, s), 12.35(1H, s).

MS: 526 $(M+H)^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-{2-[(methylsulfonyl)amino]ethyl}-1,3-thiazole-5-carboxamide hydrochloride was prepared in a similar manner according to Step 2 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.15(3H, s), 2.89(3H, s), 2.89-3.27(8H, m), 7.12(1H, t, J=5.7 Hz), 7.24(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 8.05(1H, t, J=5.4 Hz), 9.95(2H, br), 12.36(1H, s).

MS: 425 $(M+H)^+$ free

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[({2-[(methylsulfonyl)amino]ethyl}amino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.80-2.97(5H, m), 3.00-3.14(2H, m), 3.15-3.30(4H, m), 7.11(1H, m), 7.17(2H, d, J=8.5 Hz), 7.42(2H, d, J=8.5 Hz), 8.01(1H, m), 9.93(1H, s), 11.43(1H, s), 12.37(1H, s).

MS: 668 $(M+H)^+$

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

white powder

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.90-2.96(5H, m), 3.08(2H, m), 3.19-3.29(4H, q), 7.14(2H, d, J=8.3 Hz), 7.28(2H, d, J=8.3 Hz), 7.43(4H, br), 8.07(1H, m), 9.87(1H, s), 12.38(1H, s).

MS: 467 $(M+H)^+$ free

Production Example 75: Synthesis of 2-(acetylamino)-4-[2-(4-

{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(dimethylamino)-3-oxopropyl]-N-methyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[[3-(dimethylamino)-3-oxopropyl](methyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.50(9H, s), 2.14(3H, s), 2.56(2H, t, J=7.3 Hz), 2.78(3H, s), 2.84-2.88(6H, m), 2.93(3H, s), 3.47(3H, m), 7.12(2H, d, J=8.4 Hz), 7.40(2H, d, J=8.4 Hz), 9.92(1H, s), 11.43(1H, s), 12.34(1H, s).

MS: 659(M+Na)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.15(3H, s), 2.50-2.60(6H, m), 2.79(3H, s), 2.87(3H, s), 2.94(3H, s), 3.39-3.64(2H, m), 7.09-7.26(4H, m), 7.46(4H, br), 9.96(1H, s), 12.35(1H, s).

MS: 460(M+H)$^+$ free

Production Example 76: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-{3-[benzyl(methyl)amino]-3-oxopropyl}-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[({3-[benzyl(methyl)amino]-3-oxopropyl}amino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.83(9H, s), 1.50(9H, s),

1.98-2.15(3H, m), 2.60-2.63(2H, m), 2.80-2.90(5H, m), 3.17-3.21(2H, m), 3.42-3.47(2H, m), 4.50-4.57(2H, m), 7.12-7.43(9H, m), 7.95(1H, m), 9.93(1H, s), 11.44(1H, s), 12.4(1H, s).

MS: 722 $(M+H)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16, 2.30(3H, s), 2.64(2H, m), 2.64(2H, m), 2.80-2.90(5H, m), 3.14-3.25(2H, m), 3.43-3.47(2H, m), 4.51-4.57(2H, m), 7.08-7.42(9H, m), 8.02-8.04(1H, m), 9.83-9.87(1H, m), 12.36(1H, m).

MS: 522 $(M+H)^+$ free

Production Example 77: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-(dimethylamino)-4-oxobutyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(dimethylamino)-4-oxobutyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.50(9H, s), 1.68(2H, tt, J=6.8 Hz), 2.14(3H, s), 2.30(2H, t, J=6.8 Hz), 2.80(3H, s), 2.82-2.95(2H, m), 2.92(3H, s), 3.10-3.28(4H, m), 7.18(2H, d, J=8.5 Hz), 7.39(2H, d, J=8.5 Hz), 9.92(1H, s), 11.43(1H, br), 12.3(1H, br).

MS: 682 $(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.69(2H, m), 2.16(2H, s), 2.31(2H, t, J=7.2 Hz), 2.81(3H, s), 2.87-2.95(2H, m), 2.93(3H,

s), 3.16-3.24(4H, m), 3.57(3H, s), 7.11-7.44(4H, m), 8.06-8.23(1H, m), 9.83-9.92(1H, m), 12.35(1H, s).

MS: 460(M+H)$^+$ free

Production Example 78: Synthesis of (2R)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-N,N-dimethyl-2-pyrrolidinecarboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(2R)-2-[(dimethylamino)carbonyl]-1-pyrrolidinyl}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.50(9H, s), 1.60-1.93(3H, m), 2.06-2.30(1H, m), 2.14(3H, s), 2.66-3.14(10H, m), 3.20-3.50(2H, m), 4.89(1H, m), 7.16(2H, d, J=8.0 Hz), 7.41(2H, d, J=8.0 Hz), 9.92(1H, s), 11.41(1H, s), 12.34(1H, s).

MS: 694(M+Na)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.60-2.00(3H, m), 2.15, 2.48(3H, s x2), 2.65-3.50(12H, m), 3.60-3.75(2H, m), 7.09-7.17(2H, d x2), 7.23-7.31(2H, d x2), 7.47(3H, br), 9.94(1H, br), 12.35, 12.59(1H, s x2).

MS: 472(M+H)$^+$ free

Production Example 79: Synthesis of (2S)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-N,N-dimethyl-2-pyrrolidinecarboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(2S)-2-[(dimethylamino)carbonyl]-1-pyrrolidinyl}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(3H, s), 1.50(9H, s), 1.60-1.94(H, m), 2.14(3H, s), 2.10-2.36(1H, m), 2.67-3.11(10H, m), 3.30-3.52(2H, m), 4.88(1H, m), 7.16(2H, d, J=8.0 Hz), 7.41(2H, d, J=8.0 Hz), 9.92(1H, s), 11.41(1H, s), 12.34(1H, s).

MS: 694$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.60-2.00(3H, m), 2.15, 2.48(3H, s x2), 2.65-3.50(12H, m), 3.60-3.75(2H, m), 7.09-7.17(2H, d x2), 7.23-7.31(2H, d x2), 7.47(3H, br), 9.94(1H, br), 12.35, 12.59(1H, s x2).

MS: 472$(M+H)^+$ free

Production Example 80: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[2-(methylsulfonyl)ethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[2-(methylsulfonyl)ethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.57(9H, s), 2.15(3H, s), 2.87(2H, dd, J=8.8, 6.5 Hz), 3.02(3H, s), 3.19-

3.28(2H, dd, J=9.0, 5.5 Hz), 3.30-3.36(2H, m), 3.59(2H, dd, J=12.0, 6.0 Hz), 7.17(2H, d, J=8.4 Hz), 7.42(2H, d, J=8.4 Hz), 8.17(1H, s), 9.93(1H, s), 11.44(1H, s), 12.40(1H, s).

MS: 675$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.88-2.96(2H, m), 3.03(3H, s), 3.20-3.30(4H, m), 3.33-3.60(2H, m), 7.12-7.18(2H, m), 7.26-7.46(2H, d), 7.46(4H, br), 8.27(1H, t), 9.94(1H, s), 12.41(1H, s).

MS: 453$(M+H)^+$ free

Production Example 81: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-pyridinylmethyl)-1,3-thiazole-5-carboxamide dihydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[(4-pyridinylmethyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.40-1.50(18H, br), 2.15(3H, s), 2.89(2H, m), 3.22(2H, m), 4.39(2H, d, J=5.7 Hz), 7.09-7.18(2H, m), 7.32-7.44(3H, m), 7.66(1H, m), 8.43-8.62(3H, m), 9.94(1H, s), 11.44(1H, s), 12.40(1H, s).

MS: 660$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.18(3H, s), 2.92(2H, m), 3.13-3.28(2H, m), 4.63(2H, m), 7.12(2H, d, J=8.4 Hz), 7.24(2H, d, J=8.4 Hz), 7.47(4H, br), 7.93(2H, d, J=6.3 Hz), 8.88(3H,

m), 10.00(1H, s), 12.43(1H, s).

MS: 438(M+H)$^+$ free

Production Example 82: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(3-pyridinylmethyl)-1,3-thiazole-5-carboxamide dihydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[(3-pyridinylmethyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.50(9H, s), 2.16(3H, s), 2.89(2H, dd, J=8.6, 6.7 Hz), 3.22(2H, dd, J=8.6, 5.7 Hz), 4.38(2H, d, J=5.7 Hz), 7.13(2H, d, J=8.4 Hz), 7.25(2H, s x2, J=5.7 Hz), 7.41(2H, d, J=8.4 Hz), 8.50(2H, s x2, J=5.0 Hz), 8.62(1H, dd, J=5.0, 5.7 Hz), 9.93(1H, s), 11.43 (1H, s), 12.41(1H, s).

MS: 660(M+Na)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.17(3H, s), 2.92(2H, m), 3.23(2H, m), 4.56(2H, m), 7.10-7.31(4H, m), 7.45(4H, br), 8.01(1H, dd, J=8.1, 5.9 Hz), 8.82(1H, d, J=8.0 Hz), 8.84(2H, s), 8.96(1H, s), 12.45(1H, s).

MS: 438(M+H)$^+$ free

Production Example 83: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-{2-[(2-phenylacetyl)amino]ethyl}-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[({2-[(2-

phenylacetyl)amino]ethyl}amino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.88(2H, m), 3.25-3.31(6H, m), 3.38(2H, s), 7.15-7.44(7H, m), 7.32(2H, d, J=8.3 Hz), 7.98(1H, br), 8.11(1H, br), 9.93(1H, s), 11.43(1H, s), 12.35(1H, s).

MS: 730$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.90(2H, br), 3.20(6H, m), 7.11-7.31(9H, m), 7.38(3H, s), 8.06-8.16(2H, m), 9.75(1H, s), 12.33(1H, s).

MS: 508$(M+H)^+$ free

Production Example 84: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[5-(dimethylamino)-5-oxopentyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[5-(dimethylamino)-5-oxopentyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.39-1.50(4H, m), 1.57(9H, s), 2.14(3H, s), 2.29(2H, br), 2.79(3H, s), 2.84-2.94(2H, m), 2.94(3H, s), 3.15-3.23(4H, m), 7.16(2H, d, J=8.3 Hz), 7.42(2H, d, J=8.3 Hz), 7.97(1H, br), 9.93(1H, s), 11.44(1H, s), 12.35(1H, s).

MS: 696$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39-1.56(4H, m), 2.16(2H, m), 2.29(3H, s), 2.83-2.98(5H, m), 3.06-3.28(4H, m), 7.13(2H, d, J=8.5 Hz), 7.25(2H, d, J=8.5 Hz), 7.40(3H, br), 8.06(1H, br), 9.79(1H, s).

MS: 474(M+H)$^+$ free

Production Example 85: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(benzylamino)-3-oxopropyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(benzylamino)-3-oxopropyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.50(9H, s), 2.15(3H, s), 2.45(2H, t, J=7.2 Hz), 2.73(2H, m), 3.20(2H, m), 3.39(2H, m), 4.26(2H, d, J=5.8 Hz), 7.15-7.28(7H, m), 7.41(2H, d, J=8.4 Hz), 8.02(1H, t, J=5.5 Hz), 8.40(1H, t, J=5.5 Hz), 9.93(1H, s), 11.4(1H, br), 12.3(1H, br).

MS: 730(M+Na)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.41(2H, t, J=7.0 Hz), 2.90(2H, m), 3.20(2H, m), 3.39(2H, m), 3.63(2H, m), 4.27(2H, d, J=5.8 Hz), 7.11-7.37(9H, m), 7.37(4H, s), 8.09(1H, t, J=5.5 Hz), 8.43(1H, t, J=6.0 Hz), 9.74(1H, s), 12.35(1H, s).

MS: 508(M+H)$^+$ free

Production Example 86: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[6-(dimethylamino)-6-oxohexyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[6-(dimethylamino)-6-oxohexyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.13-1.50(24H, m), 2.14(3H, s), 2.24(2H, t, J=8.0 Hz), 2.78(3H, s), 2.88(2H, m), 2.92(3H, s), 3.07-3.25(4H, m), 7.16(2H, d, J=8.5 Hz), 7.42(2H, d, J=8.5 Hz), 7.95(1H, t, J=5.52 Hz), 9.94(1H, s), 11.4(1H, s), 12.3(1H, s).

MS: 710$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.27-1.34(2H, m), 1.47(4H, m), 2.16(3H, s), 2.26(2H, t, J=7.2 Hz), 2.79(3H, s), 2.94(3H, s), 2.90-2.94(2H, m), 3.17(4H, m), 7.13(2H, d, J=8.3 Hz), 7.26(2H, d, J=8.3 Hz), 7.47(4H, br), 8.05(1H, t, J=5.4 Hz), 9.93(1H, s).

MS: 488$(M+H)^+$ free

Production Example 87: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(4-morpholinyl)propyl]-1,3-thiazole-5-carboxamide dihydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(4-morpholinyl)propyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34

in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.58(9H, br), 1.62(2H, m), 2.14(3H, s), 2.31(6H, m), 2.88(2H, m), 2.19(4H, m), 3.58(4H, m), 7.14(2H, d, J=8.4 Hz), 7.41(2H, d, J=8.4 Hz), 7.95(1H, t, J=5.2 Hz), 9.94(1H, s), 11.45(1H, s), 12.30(1H, s).

MS: 696$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.90-2.00(2H, br), 2.17(3H, s), 2.83-3.15(6H, m), 3.15-3.30(4H, m), 3.30-3.44(2H, m), 3.77-4.00(4H, m), 7.14(2H, d, J=8.5 Hz), 7.26(2H, d, J=8.5 Hz), 7.44(4H, br), 8.20(1H, t, J=5.5 Hz), 9.92(1H, s), 11.01(1H, s), 12.38(1H, s).

MS: 474$(M+H)^+$ free

Production Example 88: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(2-oxo-1-pyrrolidinyl)propyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.41(9H, br), 1.49(9H, br), 1.64(2H, t, J=6.9 Hz), 1.90(2H, m), 2.14(3H, s), 2.17(2H, m), 2.91(2H, m), 3.16(6H, m), 3.32(2H, m), 7.16(2H, d, J=8.4 Hz), 7.41(2H, d, J=8.4 Hz), 7.93(1H, t, J=5.6 Hz), 9.93(1H, br), 11.73(1H, br).

MS: 694$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.65(2H, m), 1.91(2H, m), 2.16(3H, s), 2.20(2H, q, J=7.5 Hz), 2.90(2H, m), 3.02-3.27(6H, m), 3.33(2H, t, J=7.5 Hz), 7.16(2H, d, J=8.5 Hz), 7.26(2H, d, J=8.5 Hz), 8.03(1H, br), 9.92(1H, s), 12.35(1H, s).

MS: 472(M+H)$^+$ free

Production Example 89: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-hexyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(hexylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 0.85(3H, t, J=6.4 Hz), 1.25(9H, s), 1.35-1.60(17H, br), 2.14(3H, s), 2.88(2H, m), 3.15(4H, m), 7.14(2H, d, J=8.5 Hz), 7.41(2H, d, J=8.5 Hz), 7.92(1H, t, J=5.7 Hz), 10.00(1H, br), 11.60(1H, br).

MS: 653(M+Na)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6 (+D_2O)), δ (ppm): 0.86(3H, t, J=6.53 Hz), 1.18-1.57(8H, m), 2.16(3H, s), 2.91(2H, dd, J=9.5, 6.0 Hz), 3.16(4H, m), 7.13(2H, d, J=8.5 Hz), 7.25(2H, d, J=8.5 Hz), 8.05(1H, br), 9.91(1H, s), 12.33(1H, s).

MS: 431(M+H)$^+$ free

Production Example 90: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-oxo-4-(1-piperidinyl)butyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-oxo-4-(1-piperidinyl)butyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.29-1.59(20H, m), 1.69(2H, m), 2.14(3H, s), 2.30(2H, t, J=7.5 Hz), 2.89(4H, m), 3.32-3.45(4H, m), 7.16(2H, d, J=8.0 Hz), 7.41(2H, d, J=8.0 Hz), 7.99(1H, t, J=5.2 Hz), 9.94(1H, s), 11.43(1H, br).

MS: 722$(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.30-1.79(8H, m), 2.16(3H, s), 2.31(2H, t, J=7.5 Hz), 2.92(2H, m), 3.18(4H, m), 3.38(4H, m), 7.13(2H, d, J=8.0 Hz), 7.25(2H, d, J=8.0 Hz), 7.43(4H, br), 8.09(1H, t, J=6.0 Hz), 9.87(1H, s), 12.34(1H, s).

MS: 500$(M+H)^+$ free

Production Example 91: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-(4-morpholinyl)-4-oxobutyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(4-morpholinyl)-4-oxobutyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.40(9H, s), 1.50(9H, s), 1.71(2H, m), 2.14(3H, s), 2.32(2H, t, J=7.3 Hz), 2.89(2H, dd, J=10.1, 6.9 Hz), 3.19(4H, m), 3.42(4H, m), 3.51(4H, m),

7.16(2H, d, J=8.3 Hz), 7.42(2H, d, J=8.3 Hz), 7.99(2H, t, J=5.3 Hz), 9.94(1H, s), 11.44(1H, s), 12.33(1H, s).

MS: 724 $(M+Na)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.70(2H, m), 2.16(3H, s), 2.33(2H, t, J=7.0 Hz), 2.91(2H, m), 3.19(4H, m), 3.42(4H, m), 3.53(4H, m), 7.13(2H, d, J=8.5 Hz), 7.25(2H, d, J=8.5 Hz), 7.44(4H, br), 8.07(1H, t, J=5.0 Hz), 9.89(1H, s), 12.34(1H, s).

MS: 502 $(M+H)^+$ free

Production Example 92: Synthesis of 2-(acetylamino)-4-[2-({[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-(methylsulfonyl)phenyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(methylthio)phenyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.18(3H, s), 2.45(3H, s), 2.82-3.00(2H, m), 3.17-3.30(2H, m), 7.13(2H, d, J=8.5 Hz), 7.23(2H, d, J=8.5 Hz), 7.41(2H, d, J=8.5 Hz), 7.61(2H, d, J=8.5 Hz), 9.92(2H, s), 11.43(1H, s), 12.45(1H, s).

MS: 691 $(M+Na)^+$

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(methylsulfonyl)phenyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in

a similar manner according to Step 2 of Production Example 32.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.18(3H, s), 2.81-3.03(2H, m), 3.18(3H, s), 3.19-3.30(2H, m), 7.16(2H, d, J=8.5 Hz), 7.41(2H, d, J=8.5 Hz), 7.86(2H, d, J=9.0 Hz), 7.93(2H, d, J=9.0 Hz), 9.92(1H, s), 10.34(1H, s), 11.42(1H, s), 12.52(1H, s).

MS: 723(M+Na)$^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.20(3H, s), 2.84-3.07(2H, m), 3.17-3.32(2H, m), 3.18(3H, s), 7.12(2H, d, J=8.5 Hz), 7.37(4H, br), 7.86(2H, d, J=9.0 Hz), 7.92(2H, d, J=9.0 Hz), 9.76(1H, s), 10.42(1H, s).

MS: 501(M+H)$^+$ free

Production Example 93: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S)-2-(dimethylamino)-1-methyl-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[(1S)-2-(dimethylamino)-1-methyl-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.40(3H, d, J=7.0 Hz), 1.49(9H, s), 1.53(9H, s), 2.22(3H, s), 2.95(2H, m), 3.00(3H, s), 3.10(3H, s), 3.26(2H, m), 5.01(1H, dt, J=7.0 Hz), 6.87(1H, d, J=7.5 Hz), 7.14(2H, d, J=8.5 Hz), 7.40(2H, d, J=8.5 Hz), 9.57(1H, br), 10.20(1H, s), 11.62(1H, s).

MS: 646(M+H)$^+$

Step 2